SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Absorbable Coronary Drug-Eluting Stent

Device Trade Name: Absorb GT1™ Bioresorbable Vascular Scaffold (BVS) System

Device Procode: PNY

Applicant's Name and Address: Abbott Vascular
3200 Lakeside Drive
Santa Clara, CA 95054

Date(s) of Panel Recommendation: March 15, 2016

Premarket Approval Application (PMA) Number: P150023

Date of FDA Notice of Approval: July 5, 2016

II. INDICATIONS FOR USE

The Absorb GT1 Bioresorbable Vascular Scaffold (BVS) is a temporary scaffold that will fully resorb over time and is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to *de novo* native coronary artery lesions (length ≤ 24 mm) with a reference vessel diameter of ≥ 2.5 mm and ≤ 3.75 mm.

III. CONTRAINDICATIONS

The Absorb GT1 BVS System is contraindicated for use in:

- Patients who cannot tolerate, including allergy or hypersensitivity to, procedural anticoagulation or the post-procedural antiplatelet regimen.
- Patients with hypersensitivity or contraindication to everolimus or structurally-related compounds, or known hypersensitivity to scaffold components (poly(L-lactide), poly(D,L-lactide), platinum) or with contrast sensitivity.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Absorb GT1 BVS System labeling.

V. DEVICE DESCRIPTION

The Absorb GT1 Bioresorbable Vascular Scaffold (BVS) System is composed of the following components:

- A bioresorbable poly(L-lactide) (PLLA) scaffold
- A coating comprised of the active pharmaceutical ingredient everolimus and bioresorbable poly(D,L-lactide) (PDLLA)
- Four (4) platinum marker beads, two (2) embedded at both the proximal and distal ends of the scaffold for radiopacity
- A scaffold delivery system that leverages technology of the XIENCE family of products and incorporates design features from the Absorb BVS, XIENCE Xpedition®, and XIENCE Alpine® delivery systems

The product description for the Absorb GT1 BVS System is detailed below in **Table V-1**. The Absorb GT1 BVS System size matrix incorporates a small and medium scaffold design. The small design is available in 2.5 and 3.0 mm diameters in lengths of 8, 12, 18, 23, and 28 mm. The medium design is available in a 3.5 mm diameter in lengths of 12, 18, 23, and 28 mm. The Absorb GT1 BVS System is available in a Rapid Exchange (RX) configuration.

Table V-1 Absorb GT1 BVS System Product Description

<table>
<tr><td>Available Stent Lengths (mm)</td><td colspan="6">8, 12, 18, 23, and 28</td></tr>
<tr><td>Available Stent Diameters (mm)</td><td colspan="6">2.5, 3.0, and 3.5</td></tr>
<tr><td>Stent Material</td><td colspan="6">Poly(L-lactide)</td></tr>
<tr><td>Drug Component</td><td colspan="6"><table>
<tr><th>Scaffold Design</th><th>Scaffold Diameter (mm)</th><th>Scaffold Length (mm)</th><th>Scaffold Surface Area (cm^2)</th><th>Drug Dose Density ($\mu g/cm^2$)</th><th>Target Drug Amount (µg)</th></tr>
<tr><td rowspan="5">Small</td><td rowspan="5">2.5 / 3.0</td><td>8</td><td>0.76</td><td rowspan="9">100</td><td>76</td></tr>
<tr><td>12</td><td>1.14</td><td>114</td></tr>
<tr><td>18</td><td>1.81</td><td>181</td></tr>
<tr><td>23</td><td>2.28</td><td>228</td></tr>
<tr><td>28</td><td>2.76</td><td>276</td></tr>
<tr><td rowspan="4">Medium</td><td rowspan="4">3.5</td><td>12</td><td>1.35</td><td>135</td></tr>
<tr><td>18</td><td>1.97</td><td>197</td></tr>
<tr><td>23</td><td>2.46</td><td>246</td></tr>
<tr><td>28</td><td>3.08</td><td>308</td></tr>
</table></td></tr>
<tr><td>Delivery System Working Length</td><td colspan="6">143 cm</td></tr>
<tr><td>Delivery System</td><td colspan="6">Single access port to inflation lumen; guide wire exit notch is located 26 cm from tip; designed for guide wires ≤ 0.014”.</td></tr>
<tr><td>Scaffold Delivery System Balloon</td><td colspan="6">A compliant, tapered balloon, with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded scaffold length</td></tr>
</table>

Table V-1 Absorb GT1 BVS System Product Description

<table>
<tr><td>Balloon Inflation Pressure</td><td>Rated Burst Pressure (RBP): 16 atm (235 psi)<table><tr><th>Stent Diameter (mm)</th><th>In vitro Stent Nominal Pressure (atm)</th></tr><tr><td>2.5</td><td>6</td></tr><tr><td>3.0</td><td>7</td></tr><tr><td>3.5</td><td>6</td></tr></table></td></tr>
<tr><td>Guiding Catheter Inner Diameter</td><td>≥ 6 F (0.066”)</td></tr>
<tr><td>Catheter Shaft Outer Diameter</td><td>Distal: 0.039” ± 0.002” (0.99 mm ± 0.05 mm)
Proximal: ≤ 0.029” (0.74 mm)</td></tr>
</table>

A. Device Component Description

The Absorb GT1 BVS System consists of a polymeric scaffold mounted on a scaffold delivery system (SDS). The scaffold is manufactured from the bioresorbable polymer poly(L-lactide) (PLLA), a semicrystalline polymer whose degree of crystallinity and crystalline microstructure are dictated by the thermal and deformation history during processing. Two (2) platinum markers are embedded at each end ring to enable fluoroscopic visualization.

The SDS incorporates design features from the Absorb BVS, XIENCE Xpedition, and XIENCE Alpine delivery systems. The delivery system has a rapid-exchange (RX) design with the balloon and scaffold at the distal end of the catheter. For the RX design, the proximal lumen provides for inflation of the balloon with contrast medium and the central distal lumen permits a guidewire to facilitate advancement of the catheter. The distal catheter shaft, the tip, and tapers of the balloon are coated with HYDROCOAT™ Hydrophilic Coating.

Radiopaque markers are positioned underneath the balloon to provide accurate positioning of the scaffold / balloon in the artery. The balloon is designed to deliver an expandable scaffold of known diameter and length at specified pressures. Markers located on the proximal outer shafts help physicians gauge the delivery catheter position relative to the guiding catheter tip. An adaption arm on the proximal end provides access to the inflation lumen. The SDS is designed with a luer-lock fitting to facilitate connection to an inflation device.

B. Drug Component Description

The Absorb GT1 BVS is coated with a drug / polymer matrix that consists of 50 wt% PDLLA and 50 wt% of the active pharmaceutical ingredient everolimus, the same drug utilized for the XIENCE family of products. Neither a primer coat nor a topcoat layer is utilized for the Absorb GT1 BVS. The Absorb GT1 BVS also utilizes the same drug dose density (100 $\mu g/cm^2$) and similar coating technologies as the XIENCE family of products.

B1. Everolimus

Everolimus (Chemical name: 40-O-(2-hydroxyethyl)-rapamycin) (**Figure V-1**) is a novel semisynthetic macrolide immunosuppressant obtained through chemical modification of rapamycin. Rapamycin (INN: Sirolimus) is a secondary macrolide metabolite that is produced by certain actinomycete strains.

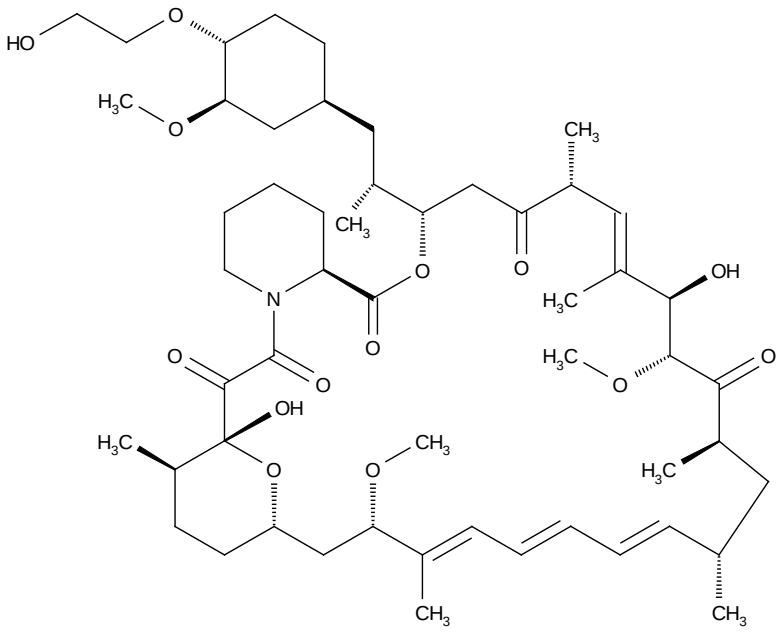


Figure V-1 Chemical Structure of Everolimus

B2. Inactive Ingredients

The Absorb GT1 BVS System contains poly(D,L-lactide) (PDLLA), an amorphous polymer containing an equimolar mixture of D- and L lactide. PDLLA is used to contain and control the release of everolimus. PDLLA is characterized by a lower tensile strength and higher elongation than poly(L-lactide) (PLLA) due to its amorphous nature.

C. Mechanism of Action

The mechanism by which the Absorb GT1 BVS inhibits neointimal growth as seen in preclinical and clinical studies has not been established. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FRAP (FKBP-12 Rapamycin Associated Protein), also known as mTOR (mammalian Target Of Rapamycin), leading to inhibition of cell metabolism, growth and proliferation by arresting the cell cycle at the late G1 stage.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of patients with coronary artery disease including exercise, diet, drug therapy, percutaneous coronary interventions (i.e., balloon angioplasty, atherectomy, bare metal stents, and drug-eluting stents), and coronary artery bypass graft (CABG) surgery. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Absorb GT1 BVS System is commercially available in the following countries:

- AUSTRIA
- BAHRAIN
- BANGLADESH
- BELGIUM
- BRAZIL
- BRUNEI
- CANADA
- CHILE
- COLOMBIA
- CZECH REPUBLIC
- DENMARK
- DOMINICAN REP.
- ESTONIA
- FINLAND
- FRANCE
- GEORGIA
- GERMANY
- HONG KONG
- HUNGARY
- IRELAND
- ITALY
- JORDAN
- KUWAIT
- LATVIA
- LEBANON
- LITHUANIA
- LUXEMBOURG
- MALAYSIA
- MALTA
- MAURITIUS
- NETHERLANDS
- NORWAY
- OMAN
- PAKISTAN
- POLAND
- PORTUGAL
- QATAR
- REUNION
- ROMANIA
- SAUDI ARABIA
- SERBIA
- SLOVAKIA
- SPAIN
- SWEDEN
- SWITZERLAND
- THAILAND
- TUNISIA
- TURKEY
- UNIT.ARAB EMIR.
- UNITED KINGDOM
- VIETNAM

The Absorb BVS System* is commercially available in the following countries:

- ARGENTINA
- AUSTRALIA
- AUSTRIA
- BAHRAIN
- BANGLADESH
- BELARUS
- BELGIUM
- BRAZIL
- BRUNEI
- BULGARIA
- CHILE
- COLOMBIA
- COSTA RICA
- CYPRUS
- CZECH REPUBLIC
- DENMARK
- DOMINICAN REP.
- EGYPT
- ESTONIA
- FINLAND
- FRANCE
- GEORGIA
- GERMANY
- GREECE
- HONG KONG
- HUNGARY
- INDIA
- INDONESIA
- IRAN
- IRAQ
- IRELAND
- ISRAEL
- ITALY
- JORDAN
- KAZAKHSTAN
- KOSOVO
- KUWAIT
- LEBANON
- LIBYA
- LITHUANIA
- LUXEMBOURG
- MALAYSIA
- MALTA
- MAURITIUS
- MEXICO
- MOROCCO
- NEPAL
- NETHERLANDS
- NEW ZEALAND

- NORWAY
- OMAN
- PAKISTAN
- PANAMA
- PHILIPPINES
- POLAND
- PORTUGAL
- QATAR
- REP. OF ARMENIA
- REUNION
- ROMANIA
- RUSSIAN FED.
- SAUDI ARABIA
- SERBIA
- SINGAPORE
- SLOVAKIA
- SOUTH KOREA
- SPAIN
- SWEDEN
- SWITZERLAND
- TAIWAN
- THAILAND
- TUNISIA
- TURKEY
- UKRAINE
- UNIT. ARAB EMIR.
- UNITED KINGDOM
- URUGUAY
- VIETNAM

*Note: The Absorb BVS System has the same scaffold as the Absorb GT1 BVS and differs from the Absorb GT1 BVS only in the delivery system.

There have been no removals of the Absorb device from commercial distribution due to safety or effectiveness reasons. There was one (1) Field Safety Notice for commercial products issued on December 7th, 2015 that highlighted updates to the Instructions For Use to improve scaffold deployment.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events that may be associated with percutaneous coronary intervention (PCI), and the use of a coronary scaffold in native coronary arteries include, but are not limited to, the following:

- Allergic reaction or hypersensitivity to latex, contrast agent, anesthesia, device materials (platinum, iridium, palladium, rhodium and gold, or polymer [poly(L-lactide) (PLLA), polymer poly(D,L-lactide) (PDLLA)]), and drug reactions to everolimus, anticoagulation, or antiplatelet drugs
- Vascular access complications which may require transfusion or vessel repair, including:
  - Catheter site reactions
  - Bleeding (ecchymosis, oozing, hematoma, hemorrhage, retroperitoneal hemorrhage)
  - Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation / rupture
  - Embolism (air, tissue, plaque, thrombotic material or device)
  - Peripheral nerve injury
  - Peripheral ischemia
- Coronary artery complications which may require additional intervention, including:
  - Total occlusion or abrupt closure
  - Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation / rupture
  - Tissue prolapse / plaque shift
  - Embolism (air, tissue, plaque, thrombotic material or device)
  - Coronary or scaffold thrombosis (acute, subacute, late, very late)

    - Stenosis or restenosis
- Pericardial complications which may require additional intervention, including:
    - Cardiac tamponade
    - Pericardial effusion
    - Pericarditis
- Cardiac arrhythmias (including conduction disorders, atrial and ventricular arrhythmias)
- Cardiac ischemic conditions (including myocardial ischemia, acute myocardial infarction, coronary artery spasm and unstable or stable angina pectoris)
- Stroke / Cerebrovascular accident (CVA) and Transient Ischemic Attack (TIA)
- System organ failures:
    - Cardio-respiratory arrest
    - Cardiac failure
    - Cardiopulmonary failure (including pulmonary edema)
    - Renal insufficiency / failure
    - Shock
- Blood cell disorders (including Heparin Induced Thrombocytopenia [HIT])
- Hypotension or hypertension
- Infection
- Nausea and vomiting
- Palpitations, dizziness, and syncope
- Chest pain
- Fever
- Pain
- Death

Zortress®, the oral formulation of everolimus developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the United States for the prevention of organ rejection in adult kidney transplant recipients at the dose of 1.5 mg/day.

Outside the U.S., Zortress is sold under the brand name Certican® in more than 70 countries. Everolimus is also approved in the United States under the name Afinitor® for patients with advanced renal cell carcinoma (cancer), after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The following list includes the known risks of everolimus at the oral doses listed above:

- Abdominal pain
- Anemia
- Angioedema (increased risk with concomitant ACE inhibitor use)
- Anorexia
- Arterial thrombotic events
- Asthenia
- Bleeding and coagulopathy
- Constipation

- Cough
- Diabetes mellitus
- Diarrhea
- Dry skin
- Dysgeusia
- Dyslipidemia (including hyperlipidemia and hypercholesterolemia)
- Dyspepsia
- Dyspnea
- Dysuria
- Embryo-fetal toxicity
- Epistaxis
- Erythema
- Erythroderma
- Fatigue
- Headache
- Hematuria
- Hepatic Artery Thrombosis (HAT)
- Hepatic disorders (including hepatitis and jaundice)
- Hypersensitivity to everolimus active substance, or to other rapamycin derivates
- Hypertension
- Infections and serious infections (bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens). Polyoma virus-associated nephropathy (PVAN), JC virus-associated progressive multiple leukoencephalopathy (PML), fatal infections, and sepsis have been reported in patients treated with oral everolimus
- Insomnia
- Interaction with strong inhibitors and inducers of CYP3A4 or PgP
- Laboratory test abnormalities (elevations of serum creatinine, proteinuria, hyperkalemia, hypokalemia, hyperglycemia, dyslipidemia including hypercholesterolemia and hypertriglyceridemia, hypomagnesemia, hypophosphatemia, abnormal liver function tests, reduction in hemoglobin, lymphocytes, neutrophils, and platelets)
- Leukopenia
- Lymphoma and other malignancies (including skin cancer)
- Male infertility (azospermia and/or oligospermia)
- Mucosal inflammation (including oral ulceration and oral mucositis)
- Nausea
- Nephrotoxicity (in combination with cyclosporine)
- Neutropenia
- Non-infectious pneumonitis (including interstitial lung disease)
- Oral ulcerations
- Pain: extremity, incision site and procedural, back, chest, musculoskeletal
- Pancreatitis
- Pericardial effusion

- Peripheral edema
- Pleural effusion
- Pneumonia
- Proteinuria
- Pruritis
- Pyrexia
- Rash
- Renal arterial and venous thrombosis
- Renal failure
- Stomatitis
- Thrombocytopenia
- Thrombotic microangiopathy (TMA)/Thrombotic thrombocytopenic purpura (TTP)/ Hemolytic uremic syndrome (HUS) – increased risk with concomitant cyclosporine use
- Tremor
- Upper respiratory tract infection
- Urinary tract infection
- Venous thromboembolism
- Vomiting
- Wound healing complications (including delayed wound healing, wound infections and lymphocele)

Live vaccines should be avoided and close contact with those that have had live vaccines should be avoided. There may be other potential adverse events that are unforeseen at this time.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

A1. Biocompatibility Studies

ISO 10993-1-specified biocompatibility tests for a blood contact permanent implant (>30 days) were performed for the Absorb GT1 BVS with everolimus (drug scaffold) and without everolimus (polymer only scaffold). These tests include cytotoxicity, sensitization, irritation or intracutaneous reactivity, systemic toxicity (acute), subchronic toxicity, genotoxicity, implantation, and hemocompatibility. The Absorb GT1 BVS passed all test acceptance criteria (**Table IX-1**).

ISO 10993-1 specified biocompatibility tests for externally communicating devices contacting circulating blood (≤ 24 hours) were performed for the Absorb GT1 BVS scaffold delivery system (SDS). These tests include cytotoxicity, sensitization, irritation or intracutaneous reactivity, systemic toxicity (acute), and hemocompatibility. The SDS passed all test acceptance criteria (**Table IX-1**).

All biocompatibility testing was conducted in accordance with one or more of the following regulations and guidance documents:

- ISO 10993 Biological Evaluation of Medical Devices
- Guidance for Industry and Food and Drug Administration Staff – Use of International Standard ISO-10993-1, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing Within a Risk Management Process"
- Good Laboratory Practices Regulations (21 CFR, part 58)

Table IX-1 Biocompatibility Test Summary

Test	Test Description	Test Article and Results
Cytotoxicity	ISO 10993-5: MEM Extract or Direct Contact	• Drug scaffold: Pass (non-cytotoxic) • Polymer only scaffold: Pass (non-cytotoxic) • Optimized delivery system: Pass (non-cytotoxic)
Sensitization	ISO 10993-10: Maximization Test for Delayed Hypersensitivity	• Drug scaffold: Pass (non-sensitizing) • Polymer only scaffold: Pass (non-sensitizing) • Optimized Delivery System: Pass (non-sensitizing)
Intracutaneous Reactivity	ISO 10993-10: Intracutaneous (Intradermal) Reactivity Test	• Drug scaffold: Pass (non-irritating) • Polymer only scaffold: Pass (non-irritating) • Optimized delivery system: Pass (non-irritating)
Systemic Toxicity (Acute)	ISO 10993-11:Acute Systemic Toxicity	• Drug scaffold: Pass (non-toxic) • Polymer only scaffold: Pass (non-toxic) • Optimized delivery system: Pass (non-toxic)
	ISO 10993-11 and USP <151>: Pyrogen Test (Material Mediated)	• Drug scaffold: Pass (non-pyrogenic) • Polymer only scaffold: Pass (non-pyrogenic) • Optimized delivery system: Pass (non-pyrogenic)

Table IX-1 Biocompatibility Test Summary

Test	Test Description	Test Article and Results
Hemocompatibility	ISO 10993-4: Hemolysis Direct and Indirect Contact	• Drug scaffold: Pass (non-hemolytic) • Polymer only scaffold: Pass (non-hemolytic) • Optimized Delivery System: Pass (non-hemolytic)
	ISO 10993-4: Coagulation (PT and PPT)	• Drug scaffold: Pass • Polymer only scaffold: Pass • Optimized delivery system: Pass
	ISO 10993-4: Complement Activation (C3a and SC5b-9)	• Drug scaffold: Pass • Polymer only scaffold: Pass • Optimized delivery system: Pass
Implantation	ISO 10993-11: Subchronic Toxicity - 90 day implantation	• Polymer only scaffold: Pass (non- toxic)
Genotoxicity	ISO 10993-3: Bacterial Reverse Mutation Assay (AMES Test)	• Drug scaffold: Pass (non-mutagenic) • Polymer only scaffold: Pass (non-mutagenic)
	ISO 10993-3: *In Vitro* Chromosomal Aberration	• Drug scaffold: Pass (non-mutagenic) • Polymer only scaffold: Pass (non-mutagenic)
	ISO 10993-3: Clastogencity in Mammalian Cells (Forward Mutation)	• Drug scaffold: Pass (non-mutagenic) • Polymer only scaffold: Pass (non-mutagenic)
	ISO 10993-3: Mammalian Erythrocyte Micronucleus Test	• Drug scaffold: Pass (non-mutagenic) • Polymer only scaffold: Pass (non-mutagenic)

Since the Absorb GT1 BVS uses the identical drug substance (everolimus) as the XIENCE family of stents at the same drug dose density of 100 µg/cm^2, carcinogenicity and teratology studies in the original XIENCE V PMA submission (P070015) were leveraged for the Absorb GT1 BVS. Degradation characterization and impact on biocompatibility were assessed with long term preclinical studies (up to 48 months) in porcine coronary arteries. All the studies met pre-specified study acceptance criteria and support the biocompatibility of the Absorb GT1 BVS.

A2. *In Vitro* Engineering Testing

In vitro engineering testing, in accordance with the April 2010 FDA "Guidance for Industry and FDA Staff – Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems," was conducted on the Absorb GT1 BVS System. This testing is summarized in **Table IX-2**. "Pass" denotes that the test results met product specifications and/or the recommendations in the above referenced guidance document.

Table IX-2 *In Vitro* Engineering Testing

Test	Test Description	Results
Scaffold Dimensional and Functional Testing		
Uniformity of Expansion (UoE)	Determines the uniformity of expansion along the scaffold length following nominal deployment.	PASS
Scaffold Percent Length Change	Determines the difference in scaffold length pre-and post-expansion following nominal or post-dilated deployment.	PASS
Percent Recoil	Determines the amount of recoil by which the outer diameters of the scaffold decreases from its expanded diameter on the inflated delivery balloon to its relaxed diameter after deflating the balloon following nominal and post-dilated deployment.	PASS
Circumferential Radial Strength	Determines the radial force or pressure required to permanently deform the deployed scaffold following nominal and post-dilated deployment.	PASS
Radial Stiffness	Determines the radial stiffness of the deployed scaffold following nominal and post-dilated deployment.	For Characterization Only
Inner Scaffold Diameter Prior to Strut Fracture / Post-Dilate to Fracture (PDTF)	Determines the limit for expansion before strut fracture.	PASS
Maximum Crossing Profile Diameter	Determines the crossing profile / crimped scaffold outer diameter.	PASS
Minimum Scaffold Dislodgement Force (Distal)	Determines the minimum force required to dislodge the scaffold from the delivery system in the distal direction.	PASS
Minimum Scaffold Dislodgement Force (Proximal)	Determines the minimum force required to dislodge the scaffold from the delivery system in the proximal direction.	PASS
Nominal Scaffold ID	Determines the scaffold inner diameter (ID) when the device is inflated to nominal balloon pressure.	PASS

Table IX-2 *In Vitro* Engineering Testing

Test	Test Description	Results
Scaffold Markers (Marker Verification)	Verifies the presence of the scaffold markers (marker beads) after subjecting the system to an environment similar to that seen in routine use, including post-dilated deployment.	PASS
Visual Inspection / Scaffold Placement	Visually inspects a scaffold and scaffold delivery system and verifies there is no damage to the scaffold and verifies the scaffold placement while in the crimped state.	PASS
Pullback into Guiding Catheter	Determines the ability of the un-deployed system to be withdrawn into a guiding catheter.	PASS
Scaffold Dimensions (Ring Strut Width and Tube Wall Thickness)	Measures dimension tolerances for the uncoated, as cut, pre-sterile scaffold.	PASS
Scaffold Percent Surface Area	Scaffold Percent Surface Area (scaffold-artery ratio) was determined using a theoretical calculation based on the scaffolded vessel area and a 3D computational model of the scaffold design.	For Characterization Only
Radiopacity	Evaluated the ability to visualize the Absorb GT1 BVS System using fluoroscopy during scaffold delivery, deployment, and after implementation.	PASS

Table IX-2 *In Vitro* Engineering Testing

Test	Test Description	Results
Magnetic Resonance Imaging (MRI) Safety and Compatibility	Non-clinical testing has demonstrated the Absorb GT1 BVS is MR Conditional (as defined in ASTM F2503-13). A patient with this device can be safely scanned in all MR environments 3T or less. RF-Induced Heating of Tissue around Absorb GT1 BVS • Experimental data demonstrates that RF-induced heating is minimal. The temperature rise due to RF heating of the Absorb GT1 BVS is similar to that of the background rise with no implant as tested at 1.5T and 3.0T MRI systems per ASTM F2182-11a. • Scientific Rationale indicates that Absorb GT1 BVS has minimal RF-induced heating based on both temperature rise and energy deposition calculations. Magnetically Induced Displacement Force • Experimental data demonstrate that the magnetic force measured per ASTM F2052-14 on the Absorb GT1 BVS is minimal. • Scientific Rationale indicates that the calculated magnetically induced displacement force on the platinum marker beads is less than its weight in any conceivable (20T) MR system. The marker beads thus meet the safety criterion that magnetic force not exceed the implant weight. Magnetically Induced Torque • Experimental data demonstrate that magnetically induced torque on the Absorb GT1 BVS is minimal since force on the Absorb GT1 BVS does not exceed its weight and the Absorb GT1 BVS does not move before and after entering the magnetic field (3T system). • Scientific Rationale indicates that the calculated worst case torque ratio is 0.256. The torque ratio on the marker beads is less than the gravity value for any conceivable MR system (20T). Image Artifacts • Experimental data demonstrate that image artifacts on Absorb GT1 BVS are minimal per ASTM F2119-07 (reapproved 2013).	PASS
Scaffold Mechanical Properties	Uniaxial tensile testing was performed to characterize the mechanical properties of PLLA expanded tubing used to manufacture the scaffold.	For Characterization Only
Longitudinal Scaffold Compression	Determines the total longitudinal scaffold compression when axially loaded.	For Characterization Only

Table IX-2 *In Vitro* Engineering Testing

Test	Test Description	Results
Accelerated Structural Fatigue	Testing conducted to demonstrate structural durability of the scaffold under expected *in vivo* cyclic loading conditions for an equivalent of 1 year (~40 million cycles) in an overlapped configuration on a static bend with a radius of 15 mm.	PASS
Delivery System Dimensional and Functional Testing		
Inner Member Lumen Collapse Pressure	Determines if Inner Member (IM) collapse is reversible at negative pressure after inflation to specified pressures for the scaffold delivery systems.	PASS
Balloon Shoulder to Marker Alignment	Determines the distance between the balloon shoulder and marker for the scaffold delivery system.	PASS
Minimum Balloon Working Length	Determines the minimum balloon working length measurement of the scaffold delivery system.	PASS
Guidewire Lumen Dimensions	Measures the guidewire lumen dimensions for the scaffold delivery system.	PASS
Balloon Rated Burst Pressure	Statistically demonstrates with 95% confidence that at least 99.9% of Absorb GT1 BVS Systems will not rupture below the rated burst pressure (RBP).	PASS
Maximum Label Compliance Pressure	Statistically demonstrates with 95% confidence that at least 99% of Absorb GT1 BVS Systems will not rupture below the maximum labeled compliance (MLC) pressure.	PASS
Balloon Fatigue Resistance	Statistically demonstrates with 95% confidence that at least 90% of Absorb GT1 BVS Systems will sustain 10 repeated inflations to the rated burst pressure.	PASS
Balloon Deflation Time	Measures the inflation and deflation time of a balloon from a given pressure.	PASS
Catheter Preparation	Determines the number of double negative aspiration procedures necessary to displace air from the balloon with contrast medium.	PASS
Catheter Body and Proximal Adaption Pressure Integrity	Determines the pressure at which the catheter shaft inflation lumen and proximal adaption fail for a scaffold delivery.	PASS
Catheter Flexibility and Kink	Determines the minimum radius of curvature at which the system fails.	PASS
Tip Entry Outer Diameter	Measures the entry profile of the scaffold delivery system catheter tip.	PASS

Table IX-2 *In Vitro* Engineering Testing

Test	Test Description	Results

Dimensional Specifications	Measures the dimensions of the scaffold delivery system:
	• Tip Dimension
	  o Tip Length
	• Mid-Catheter Junction Dimension
	  o Notch OD
	• Shaft Dimensions
	  o Distal Shaft OD
	  o Proximal Shaft OD
	• Proximal Shaft Marker Locations
	  o Femoral Marker
	  o Brachial Marker
	• Catheter Length
	  o Total Catheter Length
	  o Distal Catheter Length
		PASS

Catheter Tensile Strength	Determines the bond strength of a scaffold delivery system at the following locations: Proximal Balloon Seal, Notch Seal / Outer Member to Hypotube Seal, Proximal Adaption, and Soft Tip.	PASS
Hydrophilic Coating (Dry Adhesion)	Determines the adhesion of the hydrophilic coating on the scaffold delivery system shaft.	PASS
Hydrophilic Coating (Coating Coefficient of Friction)	Determines the kinetic coefficient of friction of hydrophilically-coated shafts of the scaffold delivery system.	PASS
Catheter Torque	Determines the rotation number required to break joints and/or materials or to lose functional integrity for the scaffold delivery system.	PASS
Hydrophilic Coating Integrity (Visual Inspection)	A visual assessment of the catheter coating integrity on the surface of the catheters before and after simulated use conditioning of a scaffold delivery system.	For Characterization only
Delivery, Deployment, and Retraction (DDR)	Confirms that the system is able to safely and reliably deliver the scaffold to the intended location according to the instructions for use, without damage to the scaffold.	PASS

A3. Coating Characterization Testing

The coating characterization testing conducted on the Absorb GT1 BVS System is summarized in **Table IX-3**.

Table IX-3 Coating Characterization Testing

Test	Test Description	Results
Coating Integrity	Determines the percent compromised surface area of the scaffold following post-dilated deployment	PASS
Particulate Matter by Tracking Method	Determines the particulate matter generated during simulated tracking and deployment of the scaffold at RBP.	PASS
Particulate Matter by Beaker Method	Determines the particulate matter generated during deployment and over expansion of the scaffold in a beaker of water.	For Characterization Only
Particulate Matter by Tracking Method (Overlap Configuration)	Determines the particulate matter generated during simulated tracking and deployment of two scaffolds in an overlapped configuration at RBP.	For Characterization Only
Accelerated Embolic and Coating Fatigue (Overlap Configuration)	Testing conducted to demonstrate coating durability of the Absorb GT1 BVS System under expected *in vivo* cyclic loading conditions for an equivalent of 1 year (~40 million cycles) in an overlapped configuration on a static bend with a radius of 15 mm.	For Characterization only
Acute Particulate Chemical Characterization	Testing conducted to provide chemical characterization for the particulates generated from the system using the particulate matter by tracking method.	For Characterization only
Embolic Fatigue Particulate Chemical Characterization	Testing conducted to provide chemical characterization for the particulates generated from the scaffold during embolic fatigue characterization.	For Characterization only
Coating Physical Structure and Chemical Properties	Characterizes various aspects of the coated scaffold, including: • Intra-scaffold coating uniformity • Coating adhesion • Coating thickness • Coating morphology • Coating adhesion after balloon rupture	For Characterization only

A4. Chemistry, Manufacturing & Controls (CMC) Testing

Where applicable, International Conference on Harmonisation (ICH) Guidelines were followed for the testing routinely performed on the Absorb GT1 BVS System as part of the finished product release. This testing is summarized in **Table IX-4**. Information to support the stability of the Absorb GT1 BVS System is summarized separately in **Section IX.A5 Stability/Shelf Life**.

Table IX-4 Absorb GT1 BVS System Analytical Release Testing

Test	Test Description
Appearance	A visual inspection is conducted to verify that the appearance of the Absorb GT1 BVS System meets the specification established for finished product release.
Identity	Assays are conducted to verify the identity of the drug substance, everolimus, on the Absorb GT1 BVS System using two different methods.
Total Content	Assay is conducted to quantitatively verify that the total amount of drug on the Absorb GT1 BVS System meets the specification established for finished product release.
Content Uniformity	Multiple scaffolds are tested to verify that the uniformity of the drug content between individual scaffolds meets the specification established for finished product release.
Degradation Products / Impurities	Assays are conducted to quantitatively verify the amount and type of degradation products / impurities meet the specification established for finished product release.
Particulate Matter *by Tracking Method*	The amount of particulate matter generated during simulated use is verified to meet the specification established for finished product release.
USP <85> Bacterial Endotoxins Test	The amount of bacterial endotoxins is verified to meet the specification established for finished product release.
In Vitro Drug Release	The *in vitro* drug release profile of the drug substance, everolimus, is verified to meet the specification established for finished product release.
Residual Solvent (Acetone)	The amount of residual solvent, acetone, is verified to meet the specification established for finished product release.
Number Average Molecular Weight *(M_n)*	The number average molecular weight is verified to meet the specification established for finished product release.
Sterility	Product is released by verifying that the dose complied with validated sterilization parameters and satisfies the requirement for labeling the finished product as sterile.
BHT Content	The amount of BHT is verified to meet the specification established for finished product release.

A5. Stability / Shelf Life

A formal stability study was conducted to establish a shelf life / expiration date for the Absorb GT1 BVS System. The stability attributes, including Appearance, Total Content, Degradation Products / Impurities, Particulate Matter by Tracking Method, *In Vitro* Drug Release, Number Average Molecular Weight (M_n), Whole Package Integrity

Leak Test (bubble test, in lieu of Sterility), and BHT Content were performed at each of the preselected stability time points. Tests for Identification, Content Uniformity, Residual Solvent (Acetone), and Sterility by Dosimetry were performed for initial lot release only and were not monitored during stability. USP <85> Bacterial Endotoxin Test, required for initial lot release only, was also performed every 6 months for the long-term storage condition (25°C/60%RH) of the formal stability study for informational purposes only. Testing to establish container closure integrity was conducted to ensure that sterility was maintained during the shelf life of the product. Functional testing of the Absorb GT1 BVS System was conducted on aged product. The data generated to-date support a shelf life of 12 months for the Absorb GT1 BVS System.

A6. Sterilization

The Absorb GT1 BVS System is sterilized by means of electron-beam (e-beam) radiation to meet a Sterility Assurance Level (SAL) of 10^{-6} in accordance with EN ISO 11137-1:2006 / Amd1:2013, Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices. Pursuant to the validation requirements, the Absorb GT1 BVS System has been successfully qualified for one time e-beam sterilization. In addition, the amount of bacterial endotoxins was verified to be within the specification limits.

B. Animal Studies

A series of GLP *in vivo* studies were conducted in the porcine coronary artery model in order (a) to evaluate the *in vivo* pharmacokinetic profile, (b) to evaluate the *in vivo* degradation profile, and (c) to demonstrate the *in vivo* safety of the Absorb GT1 BVS System.

The *in vivo* testing was conducted in accordance with one or more of the following general regulations, guidance documents, and consensus documents:

- Good Laboratory Practices Regulations (21 CFR § 58)
- Guidance for Industry and FDA Staff: General Considerations for Animal Studies for Cardiovascular Devices CDRH. Rockville, MD, 2010
- Guidance for Industry and FDA Staff: – Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, 2005
- Schwartz, R. S., et al. “Drug-Eluting Stents in Preclinical Studies: Updated Consensus Recommendations for Preclinical Evaluation.” Circ Cardiovasc Intervent 1(2): 143-153, 2008.
- Schwartz, R. S., et al. “Drug-eluting stents in preclinical studies: recommended evaluation from a consensus group.” Circulation 106(14): 1867-1873, 2002.

B1. *In Vivo* Pharmacokinetics

Three (3) GLP *in vivo* pharmacokinetics (PK) studies were conducted in porcine coronary arteries in order to determine the *in vivo* PK profile of everolimus for the Absorb GT1 BVS System. The first of these studies included two (2) PK studies of up to 90 days duration in which consistency in the *in vivo* pharmacokinetics profiles between Absorb BVS (manufactured in Mountain View) and Absorb BVS (manufactured in Temecula) was demonstrated. The third study included time points up to 300 days and illustrated the complete profile of everolimus elution, and through biostatistical analysis, demonstrated the bioequivalence in drug elution profiles between the Absorb GT1 BVS and the XIENCE V stent, both of which share the same drug dose density of everolimus (100 µg/cm^2). Summaries of the *in vivo* PK studies conducted to support product safety are provided in **Table IX-5**.

B2. *In Vivo* Degradation

Three (3) GLP *in vivo* degradation studies were conducted in porcine coronary arteries in order to determine the *in vivo* degradation profile for the Absorb GT1 BVS. These studies are inclusive of time points through 42 months, with results demonstrating complete scaffold resorption by approximately 36 months. A summary of the *in vivo* degradation studies conducted to support product safety is provided in **Table IX-5**.

B3. *In Vivo* Safety

Seven (7) GLP *in vivo* safety studies were conducted in the porcine coronary artery model in order to demonstrate the *in vivo* safety of the Absorb GT1 BVS. These studies are inclusive of acute (3 days), subchronic (28, 90 days), and chronic (180 days and 12 to 48 months) time points to illustrate the safety of Absorb BVS from implant to beyond complete resorption with multiple interim time points assessed throughout the resorption period. In addition, two (2) of these seven *in vivo* safety studies were conducted to demonstrate the safety of Absorb GT1 BVS in an overlapping configuration at 28 and 90 days. These studies used XIENCE V (in single and overlapping configurations) as the control article. A summary of the *in vivo* safety studies conducted to support product safety is provided in **Table IX-5**.

Table IX-5 GLP *In Vivo* PK, Degradation, and Safety Studies Conducted for the Absorb GT1 BVS System

Study Number (Designation)	Test/Control Articles	Animal Model	Number	Follow-up Duration	Endpoints
Pharmacokinetics R0100315QWB (PK-90a)	Test: Absorb BVS (mfg MTV) Control: none	Farm swine (n = 3/time point); RCA, LAD, LCX, 1 scaffold per artery with 2-3 scaffolds/ animal	Test: 6-7 scaffolds per time point Control: N/A	3 hours, 1, 3, 7, 14, 28, 60 and 90 days	Characterization of *in vivo* pharmacokinetics: drug release, blood and tissue drug concentrations.
Pharmacokinetics R0110825QWB (PK-90b)	Test: Absorb BVS (mfg TEM) Control: none	Farm swine (n = 3/time point); RCA, LAD, LCX, 1 scaffold per artery with 2-3 scaffolds/ animal	Test: 7-9 scaffolds per time point Control: N/A	3 hours, 1, 3, 7, 14, 28, 60 and 90 days	Characterization of *in vivo* pharmacokinetics: drug release, blood and tissue drug concentrations.
Pharmacokinetics R01130812QWB (PK-300)	Test: Absorb BVS (mfg TEM) Control: none	Farm swine and Yucatan mini-swine (n = 3/time point); RCA, LAD, LCX, 1 scaffold per artery with 2-3 scaffolds/ animal	Test: 6-8 scaffolds per time point Control: N/A	3 hours, 1, 3, 7, 14, 28, 60, 90, 180, and 300 days	Characterization of *in vivo* pharmacokinetics: drug release, blood and tissue drug concentrations. Bioequivalence in drug release to XIENCE V.
Polymer Degradation R0100610JCP (D-28)	Test: Absorb BVS (mfg MTV) Control: none	Farm swine (n = 5); RCA, LAD, LCX, 1 scaffold per artery with 2-3 scaffolds/ animal	Test: 12 scaffolds Control: N/A	28 days	Characterization of *in vivo* degradation profile with respect to M_n, mass loss, and PDI

Table IX-5 GLP *In Vivo* PK, Degradation, and Safety Studies Conducted for the Absorb GT1 BVS System

Study Number (Designation)	Test/Control Articles	Animal Model	Number	Follow-up Duration	Endpoints
Polymer Degradation R0100223JCP (D-90-180)	Test: Absorb BVS (mfg MTV) Control: none	Farm swine (n = 4, 90 days) and Yucatan mini-swine (n = 6, 180 days); RCA, LAD, LCX, 1 scaffold per artery with 2-3 scaffolds/ animal	Test: 12 (90 days), 14 (180 days) scaffolds per time point Control: N/A	90 and 180 days	Characterization of *in vivo* degradation profile with respect to M_n, mass loss, and PDI
Polymer Degradation R0090623JCP (D-12-42)	Test: Absorb BVS (mfg MTV) Control: none	Yucatan mini-swine (n = 3-6 per time point); RCA, LAD, LCX, 1 scaffold per artery with 2-3 scaffolds/ animal	Test: 8 - 12 per time point Control: N/A	12, 18, 24, 30, 36, and 42 months	Characterization of *in vivo* degradation profile with respect to M_n, mass loss, and PDI
Safety R110906JJB (S-28)	Test: Absorb BVS (mfg TEM) Control: XIENCE V	Farm swine (n = 9); RCA, LAD, LCX; 1 device/artery; 1-2 test and 1 control/ animal	Test: 12 Control: 9	28 days	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM • (Histomorphometry, OCT, IVUS)
Safety R110822JJB (S-90)	Test: Absorb BVS (mfg TEM) Control: XIENCE V	Farm swine (n = 10), RCA, LAD, LCX; 1 device/artery; 1-2 test and 1 control/ animal	Test: 14 Control: 10	90 days	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM • (Histomorphometry, OCT, IVUS)

Table IX-5 GLP *In Vivo* PK, Degradation, and Safety Studies Conducted for the Absorb GT1 BVS System

Study Number (Designation)	Test/Control Articles	Animal Model	Number	Follow-up Duration	Endpoints
Safety R110824QWB (S-180)	Test: Absorb BVS (mfg TEM) Control: XIENCE V	Yucatan mini-swine (n = 9); RCA, LAD, LCX; 1 device/artery; 1-2 test and 1 control/ animal	Test: 12 Control: 9	180 days	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM • (Histomorphometry, OCT, IVUS)
Safety R0100222JCP (S-3-180)	Test: Absorb BVS (mfg MTV) Control: XIENCE V	Farm swine (n = 7-9, 3, 28, 90 days) and Yucatan mini-swine (n = 9, 180 days); RCA, LAD, LCX, 1 device per artery; 1-2 test and 1 control/ animal	Test: 12 - 14 Control: 7 - 9	3, 28, 90, and 180 days	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM • (Histomorphometry, OCT, IVUS)
Safety R0090622JCP (S-12-48)	Test: Absorb BVS (mfg MTV) Control: XIENCE V	Yucatan mini-swine (n = 7-13 per time point); RCA, LAD, LCX, 1 device per artery; 1-2 test and 1 control/ animal	Test: 12-21 Control:7-13	12, 18, 24, 30, 36, 42, and 48 months	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM (12 months) • (Histomorphometry, OCT, IVUS)
Overlap Safety R0090326JCP (OL-28)	Test: overlapping Absorb BVS (mfg MTV) Control: overlapping XIENCE V	Farm swine (n = 8); RCA, LAD, LCX; 1 OL pair per artery; 1-2 OL test pair and 1 OL control pair/ animal	Test: 12 pairs Control: 8 pairs	28 days	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM • (Histomorphometry, OCT)

Table IX-5 GLP *In Vivo* PK, Degradation, and Safety Studies Conducted for the Absorb GT1 BVS System

Study Number (Designation)	Test/Control Articles	Animal Model	Number	Follow-up Duration	Endpoints
Overlap Safety R0090325JCP (OL-90)	Test: overlapping Absorb BVS (mfg MTV) Control: overlapping XIENCE V	Farm swine (n = 9); RCA, LAD, LCX; 1 OL pair per artery; 1-2 OL test pair and 1 OL control pair/ animal	Test: 12 pairs Control: 9 pairs	90 days	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM • (Histomorphometry, OCT)

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a pivotal clinical study in the US and Australia under IDE G120002 to establish a reasonable assurance of safety and effectiveness of percutaneous coronary intervention with the Absorb GT1 BVS System for improving coronary luminal diameter in patients with ischemic heart disease due to *de novo* native coronary artery lesions (length ≤ 24 mm) with a reference vessel diameter of ≥ 2.5 mm and ≤ 3.75 mm. Data from this clinical study, the ABSORB III Randomized Controlled Trial (RCT), were the basis for the PMA approval decision. Safety and effectiveness information for the Absorb GT1 BVS System is also supported by data from the ABSORB Cohort B clinical trial, ABSORB EXTEND clinical trial, ABSORB II RCT, and ABSORB Japan RCT. In this document, these trials are collectively described as the "ABSORB family of clinical trials" or the "ABSORB trials." These studies evaluated Absorb performance in subjects with ischemic heart disease caused by *de novo* lesions in native coronary arteries. Major study characteristics are summarized below and listed in **Table X-1**. Results from the ABSORB III trial are presented in this section (**Section X**), and results for the supportive clinical trials are presented in **Section XI**.

The clinical investigations outlined **Section X** and **Section XI** were performed on the previous generation Absorb BVS System. The Absorb GT1 BVS has the same mode of expansion, backbone material, scaffold coating, drug density, permanent scaffold markers, and scaffold design as the Absorb BVS. The Absorb GT1 BVS differs from the Absorb BVS only in the scaffold delivery system. The Absorb GT1 scaffold delivery system utilizes the same principle of operation and materials as other Abbott Vascular RX stent / scaffold systems and coronary dilatation catheters.

Based on the identical scaffold present on both the Absorb GT1 BVS System and the Absorb BVS System, performance of the Absorb GT1 BVS can be predicted to be similar to the performance of the Absorb BVS. Within this section, the Absorb BVS and Absorb GT1 BVS System are collectively referred to as "Absorb" and the Absorb BVS and Absorb GT1 BVS are synonymously referred to as the "Absorb scaffold."

Table X-1 Overview of ABSORB Family of Clinical Trials

	ABSORB III RCT	ABSORB Cohort B	ABSORB EXTEND	ABSORB II RCT	ABSORB Japan RCT
Study Design	Multi-center Randomized (2:1) Single-blinded Active-Control	Multi-center Non-randomized	Multi-center Non-Randomized Continued Assessment	Multi-center Randomized (2:1) Single-blinded Active-Control	Multi-center Randomized (2:1) Single-blinded Active-Control
Numbers of Patients	Total: 2008 primary analysis population Absorb: 1322 XIENCE Control: 686	Total: 101 Absorb Group 1: 45 Group 2: 56	Total: 812 Absorb	Total: 501 Absorb: 335 XIENCE Control: 166	Total: 400 Absorb: 266 XIENCE Control: 134
Numbers of Enrolling Sites	193 sites for the primary analysis population	12 sites	58 sites	46 sites	38 sites
Study Geography	US and AUS	AUS, EU, NZ	AP, EU, CA, BZ	EU, NZ	JN
Vessel Size and Lesion Length	RVD: ≥ 2.5 and ≤ 3.75 mm Length: ≤ 24 mm	RVD: 3.0 mm Length: ≤ 14 mm	D_{max} ≥ 2.0 mm and D_{max} ≤ 3.3 mm Length: ≤ 28 mm	D_{max} ≥ 2.25 mm and ≤ 3.8 mm Length: ≤ 48 mm	D_{max} ≥ 2.5 mm and ≤ 3.75 mm, Length: ≤ 24 mm
# of Treated Lesions Allowed	Up to two *de novo* lesions in different epicardial vessels. No planned overlap allowed	Up to two *de novo* lesions in different epicardial vessels. No planned overlap allowed	Up to two *de novo* lesions in different epicardial vessels. Planned overlap allowed.	Up to two *de novo* lesions in different epicardial vessels. Planned overlap allowed.	Up to two *de novo* lesions in different epicardial vessels. No planned overlap allowed.
Scaffold/Stent Sizes	Diameter: 2.5, 3.0, 3.5 mm Length: 8, 12, 18, 28 mm	Diameter: 3.0 mm Length: 18 mm	Diameter: 2.5, 3.0, 3.5 mm Length: 12, 18, 28 mm	Diameter: 2.5, 3.0, 3.5 mm Length: 12, 18, 28 mm	Diameter: 2.5, 3.0, 3.5 mm Length: 8, 12, 18, 28 mm

Table X-1 Overview of ABSORB Family of Clinical Trials

	ABSORB III RCT	ABSORB Cohort B	ABSORB EXTEND	ABSORB II RCT	ABSORB Japan RCT
Primary Endpoint(s)	One-year TLF (non-inferiority)	None	None	• Change in Mean Lumen Diameter from pre- to post-nitrate infusion at 3 years (superiority) • Change in Minimum Lumen Diameter (MLD) from pre- to post-nitrate infusion at 3 years (non-inferiority, reflex to superiority)	One-year TLF (non-inferiority)
Major Secondary Endpoints	• Angina at 1 year • Target Vessel Revascularization at 1 year • All revascularization at 1 year • Diabetic subjects at 1 year • Vasoreactivity at 3 years • Change in MLA (Mean Lumen Area) at 3 years	None	None	Change in MLA (Mean Lumen Area) at 3 years	• Late loss at 13 months • Vasoreactivity at 3-years • Change in MLA (Mean Lumen Area) at 3-years
Post Procedure Antiplatelet Therapy	Clopidogrel, prasugrel or ticagrelor 12 months minimum (per site standard). Aspirin for 5 years	Clopidogrel 6 months minimum (per site standard). Aspirin for 5 years.	Clopidogrel, prasugrel or ticagrelor 6 months minimum (per site standard). Aspirin for 3 years	Clopidogrel, prasugrel or ticagrelor 6 months minimum (per site standard). Aspirin for 5 years	Clopidogrel or prasugrel 12 months minimum (per site standard). Aspirin indefinitely.

Table X-1 Overview of ABSORB Family of Clinical Trials

	ABSORB III RCT	ABSORB Cohort B	ABSORB EXTEND	ABSORB II RCT	ABSORB Japan RCT
Clinical follow-up	30, 180 days, and annually 1 to 5 years	30, 180, 270 days, and annually 1 to 5 years	30, 180 days, and annually 1 to 3 years	30, 180 days, and annually 1 to 5 years	30, 180 days, and annually 1 to 5 years
Angiographic Follow-up	3 years*	Group 1: 180 days, 2 years and 5 years (n=45) Group 2: 1 year, 3 years, and 5 years (n=56)	Post-procedure and 2 years*	3 years	13 months, 2 to 4 years*
Angiography, IVUS and/or OCT Follow-up	3 years*	Group 1: 180 days, 2 years and 5 years(n=45) Group 2: 1 year, 3 years and 5 years (n=56)	Post-procedure and 2 years*	3 years	2 to 3 years*
PK Study	Yes (12 subjects; US)	None	None	None	None
Status	Completed enrollment. Follow-up through 1 year completed. Follow-up through 5 years ongoing.	Completed enrollment and follow-up.	Completed enrollment. Follow-up through 1 year completed. Follow-up through 3 years ongoing.	Completed enrollment. Follow-up through 1 year completed. Follow-up through 5 years ongoing	Completed enrollment. Follow-up through 1 year completed. Follow-up through 5 years ongoing.

AP, Asia Pacific; AUS, Australia; BZ, Brazil; CA, Canada; EU, Europe; JN, Japan; NZ, New Zealand; US, the United States of America
*Imaging sub-group. Three-year follow-up imaging data are not available to date.
**On a subset of patients that were available for follow-up

A. Study Design

The ABSORB III Randomized Controlled Trial (ABSORB III) is a prospective, multi-center study, registering 2,230 subjects. The primary objective of ABSORB III is to evaluate the safety and effectiveness of Absorb compared to XIENCE in the treatment of subjects, including those with diabetes mellitus, with ischemic heart disease caused by up to two *de novo* native coronary artery lesions in separate epicardial vessels. The ABSORB III trial includes the following 4 study groups:

Lead-in Group (24 subjects)

A non-randomized group to evaluate the applicability and transferability of the didactic Absorb physician training plan to United States (US) clinical practice in up to 50 subjects. The registration of the ABSORB Lead-in subjects began on December 28, 2012 and was completed on April 1, 2013. The clinical outcomes in Lead-in subjects do not contribute to the ABSORB III primary endpoint.

Primary Analysis Group (2,008 subjects)

This is a randomized (2:1 Absorb to XIENCE), single-blind study designed to support US approval of Absorb by showing non-inferiority of Absorb compared to XIENCE in 1-year target lesion failure (TLF). The first randomized subject was treated on March 22, 2013 and the last subject was treated on April 3, 2014. Results from the ABSORB III primary analysis group are presented in this section

Imaging Cohort (186 subjects)

A randomized (2:1 Absorb to XIENCE) sub-study to evaluate long-term vascular function and patency of Absorb-treated arteries compared to XIENCE-treated arteries. Three-year follow-up imaging data are not available to date.

Pharmacokinetic (PK) Group (12 subjects)

A prospective, open-label, unblinded sub-study to determine the pharmacokinetics of everolimus delivered by Absorb in subjects who only receive Absorb with a maximum of two *de novo* native coronary artery lesions after implantation of Absorb. The clinical outcomes in PK subjects do not contribute to the ABSORB III primary endpoint. The first PK subject was treated on June 2, 2014 and the subject was treated on September 17, 2014. Results from the pharmacokinetic analysis can be found in **Section X.D4 – Pharmacokinetics – ABSORB III PK**.

ABSORB IV Randomized Controlled Trial

ABSORB IV is a prospective randomized controlled trial (RCT) that began enrollment after completion of the enrollment of the ABSORB III trial primary analysis subject

cohort. ABSORB IV will enroll 3,000 subjects, randomized 1:1 to the BVS or the XIENCE stent. The study inclusion and exclusion criteria are generally similar to ABSORB III. A landmark analysis will pool ABSORB IV subjects with the 2,008 subjects from the ABSORB III primary analysis group. As of February 2016, 1,498 ABSORB IV subjects have been randomized. Enrollment is expected to be complete in December 2016.

The database for this PMA reflect data collected through April 2, 2015 and includes 2008 Primary Analysis Group patients and 12 PK Group patients. There were 193 investigational sites. The control group was the XIENCE family of products, an approved drug-eluting stent (DES) with similar indications for use.

The ABSORB III trial is powered for the primary endpoint of target lesion failure (TLF) at 1-year, a composite endpoint of cardiac death, myocardial infarction attributable to target vessel (TV-MI) or ischemia-driven target lesion revascularization (ID-TLR). The results presented in this clinical section are based on the ITT population, defined as subjects registered in the study at the point of randomization, regardless of the treatment actually received. ITT subjects are analyzed in the treatment group to which they were randomized.

The primary endpoint was TLF at 1 year was also evaluated in the pre-specified Per-Treatment Evaluable (PTE) population, defined as subjects with no major protocol deviations treated with only Absorb or XIENCE at the target lesion, with the analysis based on the treatment (Absorb or XIENCE) actually received.

The primary endpoint of TLF at 1 year is evaluated using the difference in event rates. The hypothesis test is designed to show *non-inferiority* of Absorb to XIENCE for the primary endpoint with a one-sided alpha of 0.025. The null (H_0) and alternative (H_A) hypotheses are:

H_0: $TLF_{Absorb} - TLF_{XIENCE} \geq \Delta_{PE}$
H_A: $TLF_{Absorb} - TLF_{XIENCE} < \Delta_{PE.}$

TLF_{Absorb} and TLF_{XIENCE} are the 1-year TLF rates in the Absorb and XIENCE arms, respectively. Δ_{PE} is the non-inferiority margin (4.5%).

The likelihood score method by Farrington and Manning is performed for the NI test. A successful trial requires a p-value less than 0.025 from this NI test.

Oversight for the ABSORB III trial includes an angiographic core laboratory, clinical events committee (CEC) and data safety monitoring board (DSMB). The angiographic core laboratory was responsible for reviewing all available follow-up coronary angiograms for registered subjects, to determine if a revascularization was performed by PCI, and if so, whether or not the revascularization was related to the target lesion, the target vessel or a non-target vessel. The data from the angiographic core laboratory was provided to CEC for adjudication of stent thrombosis events. The CEC was responsible

for adjudicating specified clinical endpoints based on the specific criteria used for the categorization of clinical events. The DSMB served in an advisory role to Abbott Vascular by reviewing cumulative data from the clinical trial at prescribed intervals for the purpose of safeguarding the interests of trial participants.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the ABSORB III study was limited to patients who met the following inclusion criteria:

Subjects at least 18 years old and suitable for PCI with symptomatic myocardial ischemia with a maximum of two *de novo* native coronary artery lesions in separate epicardial vessels.

Key angiographic inclusion criteria included: lesion located in native coronary artery with reference vessel diameter (RVD) ≥ 2.5 mm and ≤ 3.75 mm by visual estimation and lesion length of ≤ 24 mm by visual estimation; visually estimated or quantitatively assessed % diameter stenosis (DS) of ≥ 50%; and TIMI flow ≥ 1.

Patients were not permitted to enroll in the ABSORB III study if they met any of the following exclusion criteria:

Lesion in left main or aorto-ostial RCA lesion (within 3 mm of ostium); excessive tortuosity (≥ two 45° angles) proximal to or within the target lesion; extreme angulation (≥ 90°) proximal to or within the target lesion; moderate or heavy calcification proximal to or within the target lesion; target vessel containing thrombus; lesion involving a bifurcation with side branch ≥ 2 mm in diameter, or side branch with either an ostial or non-ostial lesion with diameter stenosis > 50%, or a side branch requiring dilatation.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 30 ± 7 days; 180 ± 28 days; 1 year ± 28 days; 2 years ± 28 days; 3 years ± 28 days; 4 years ± 28 days; and 5 years ± 28 days post-procedure. Office visit and ECG were required for the 1-year follow-up. All other follow-up are either office visit or telephone contact.

Pre-procedure, subjects were required to receive a loading dose of ≥ 300 mg of aspirin within 24 hours prior to index procedure, regardless of whether the patient was previously taking aspirin. Subjects were also required to receive a loading dose of a P_2Y_{12} receptor antagonist within 24 hours prior to index procedure (preferred), but in all cases no greater than 1 hour after the end of the procedure. Subjects were required to receive dual antiplatelet therapy for 1 year after the index procedure. Post-procedure, the objective parameters measured during the study are presented in **Table X-2** below. Adverse events and complications were recorded at all visits.

Table X-2 ABSORB III Schedule of Events

PROCEDURE/TEST	Baseline	Baseline (within 7 days)	Pre-Procedure (within 24 hours)	Procedure	Post-Procedure	30 days (± 7 d) Telephone contact or office visit	180 days (± 28 d) Telephone contact or office visit	1 yr (± 28 d) office visit	2, 3, 4, 5 yrs (± 28 d)Telephone contact or office visit	Unscheduled visits
Subject Medical/Clinical History (Age, Sex, Risk Factors, Angina Status, Cardiac History)	✓									
Subject Informed Consent (Must be obtained prior to any study related testing or procedures)	✓									
General Inclusion/Exclusion Criteria	✓									
Angiographic Inclusion/Exclusion Criteria				✓[7]						
Pregnancy Test (if applicable)		✓								
Hgb, Platelet Count, Creatinine, HbA1c, eGFR, WBC	✓[1]									
CK and CK-MB			✓[2]		✓[3]					✓[6]
Troponin I or T										✓[6]
ECG			✓[2]		✓[4]			✓	✓[8]	✓[6]
Coronary Angiogram, IVUS or OCT				✓[7]					✓[8]	
Study device information				✓						
Per Protocol Medications[5]			✓	✓	✓	✓	✓	✓	✓	✓
Concomitant Medications	✓			✓	✓	✓	✓	✓	✓	✓
Adverse Events				✓	✓	✓	✓	✓	✓	✓
Patient Reported Outcome Instruments[9]	✓[10]					✓		✓	✓	

1. The 21 day labs should be known prior to index procedure. HbA1c is to be collected in diabetic subjects only, and its result is not needed prior to the index procedure.
2. Within 48 hours pre-procedure will be acceptable except when there is evidence of acute or recent

(<7 days) myocardial infarction or unstable angina prior to the procedure, in which case pre-procedure draws/assessments must be within 24 hours. For ECGs, 12-lead must be used. If the subject does not have a known diagnosis of AMI or unstable angina within 96 hours prior to the index procedure, assessment of cardiac enzymes may be obtained after the start of the index procedure but prior to device implantation.

3. Three draws required: 1) Pre-procedure (prior to stent deployment); 2) 6 -12 hours post-procedure; 3) 18-24 hours post-procedure or at the time of discharge as long as discharge is at or after 16 hours post-procedure (for hospitals required to discharge stable subjects prior to 16 hours, the subject may be discharged but will have to return to the enrolling institution for their second biomarker draw). If either of the post-procedure CK-MB levels are ≥ 3x ULN, serial CK and CK-MB levels must be drawn until they are falling.
4. ECG must be done between 30-90 minutes post-index procedure.
5. Prasugrel 5 or 10 mg daily, clopidogrel a minimum of 75 mg daily or ticagrelor 90 mg twice daily, must be given for a minimum of 12 months, and Aspirin ≥ 75 mg to ≤ 100 mg daily must be taken through 5 years follow up during the study, and should continue to be taken indefinitely. If a subject develops hypersensitivity to clopidogrel, prasugrel or ticagrelor, subject may be switched to ticlopidine at a dose in accordance with standard hospital practice.
6. Cardiac enzymes CK and CK-MB must be collected and ECG must be done. Troponin measurement is per site standard.
7. Baseline (prior to pre-dilatation) and final (after stenting/post dilatation) angiogram must be obtained and sent to the core laboratory. For imaging sites enrolling an imaging subject, if vessel sizing is conducted using IVUS, OCT or on-line QCA, these images must also be sent to their respective core laboratory. For subjects in imaging study group, post-implantation angiogram and IVUS, or angiogram and OCT will be conducted and images sent to their respective core laboratory. Images will be sent to respective core laboratory.
8. Subjects in the imaging study group will receive either at 3 years an angiogram, ECG, plus IVUS or OCT.
9. Patient Reported Outcome instruments (EQ-5D, SAQ, RDS, GAD-7) will be administered to the 2000 primary analysis subjects in ABSORB III only.
10. Every effort should be made to have subjects complete all four patient reported outcomes questionnaires prior to the procedure. However, in situations where this is absolutely not possible, subjects may complete them post-procedure, prior to discharge. Subjects who complete their questionnaires post-procedure should base their responses on their condition prior to the procedure.

3. Clinical Endpoints

The ABSORB III primary endpoint was TLF at 1 year, defined as the composite of: cardiac death, myocardial infarction attributable to target vessel (TV-MI), or ischemia-driven target lesion revascularization (ID-TLR), tested for non-inferiority of the BVS vs. XIENCE.

Powered secondary endpoints (tested for superiority of the BVS vs. XIENCE) were:

- Angina at 1 year
- All revascularizations at 1 year
- Ischemia-driven target vessel revascularization (ID-TVR) at 1 year

Other secondary endpoints to examine the safety and effectiveness of Absorb are listed below.

Components of composite endpoints:

- Death (cardiac, vascular, non-vascular)
- Myocardial infarction attributable to target vessel (TV-MI) or not attributable to target vessel (NTV-MI)
- Ischemia-driven or non-ischemia-driven TLR (ID-TLR, NID-TLR)
- Target vessel revascularization (ID-TVR, non ID-TVR)

Other composite Endpoints:

- Death/All MI
- Cardiac death/All MI
- Cardiac death/All MI/ID-TLR (MACE)
- Cardiac death/All MI/ID-TLR/ID-TVR, non TL (Target Vessel Failure, TVF)
- Death/All MI/All revascularization

Scaffold / Stent Thrombosis (per ARC Definition):

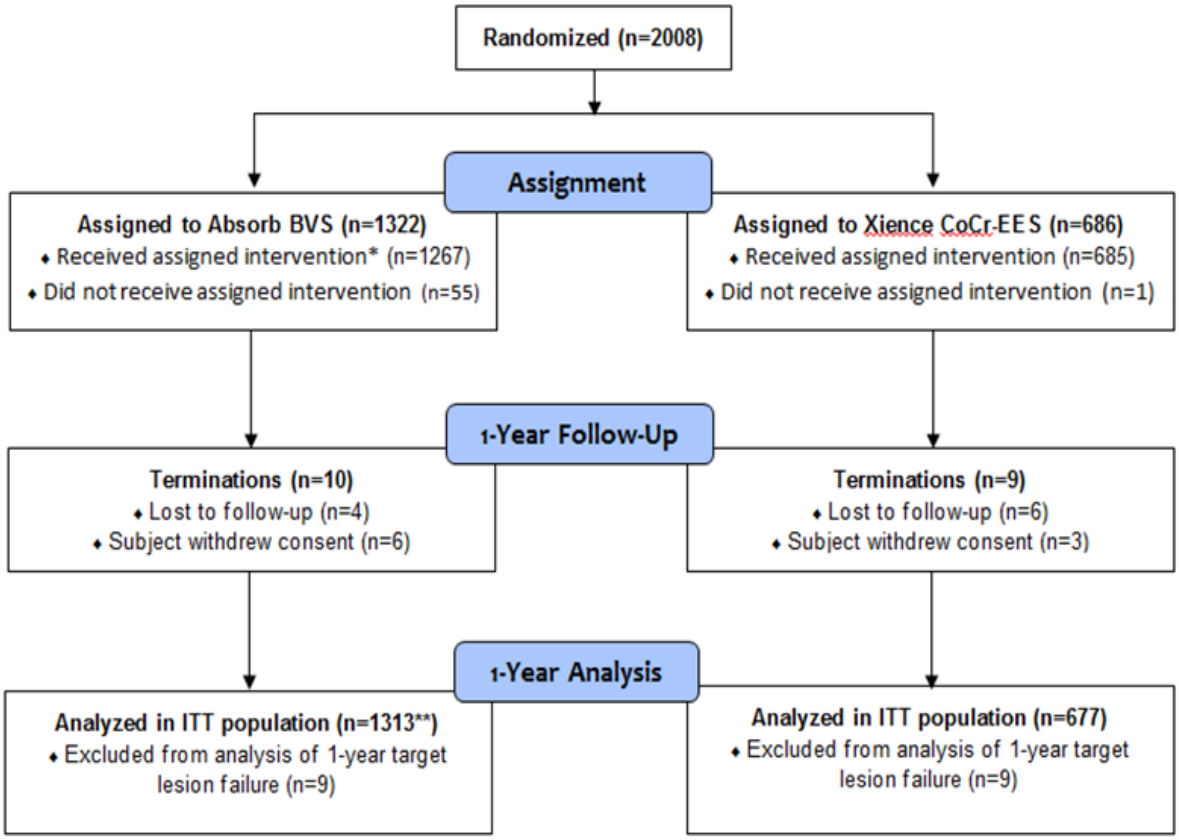
- Timing (acute, sub-acute, late and very late)
- Evidence (definite and probable)

B. Accountability of PMA Cohort

In ABSORB III, a total of 2008 (Absorb: 1322; XIENCE: 686) patients were randomized at 193 study sites, between March 22, 2013 and April 3, 2014. A total of 1385 lesions were treated in the Absorb arm, and 713 in the XIENCE arm. At the time of the database lock, of the 2008 patients enrolled in the PMA study, 99% (1990) of patients were available at the completion of the study, the 1-year post-index procedure visit: 99.3% (1313) of patients were available in the Absorb arm, and 98.7% (677) in the XIENCE arm. Early termination evaluated at 365 days, due to lost to follow-up, consent withdrawal or death, affected 1.7% (23/1322) of the subjects in the Absorb arm and 1.6% (11/686) in the XIENCE arm. All subjects have completed their 1-year follow-up and clinical follow-up through 5 years is ongoing.

Flow charts summarizing patient accountability for the ITT population, as well as the As-Treated (AT) and Per-Treatment Evaluable (PTE) populations are presented below.

Subject Flow and 1-year follow-up in ITT population

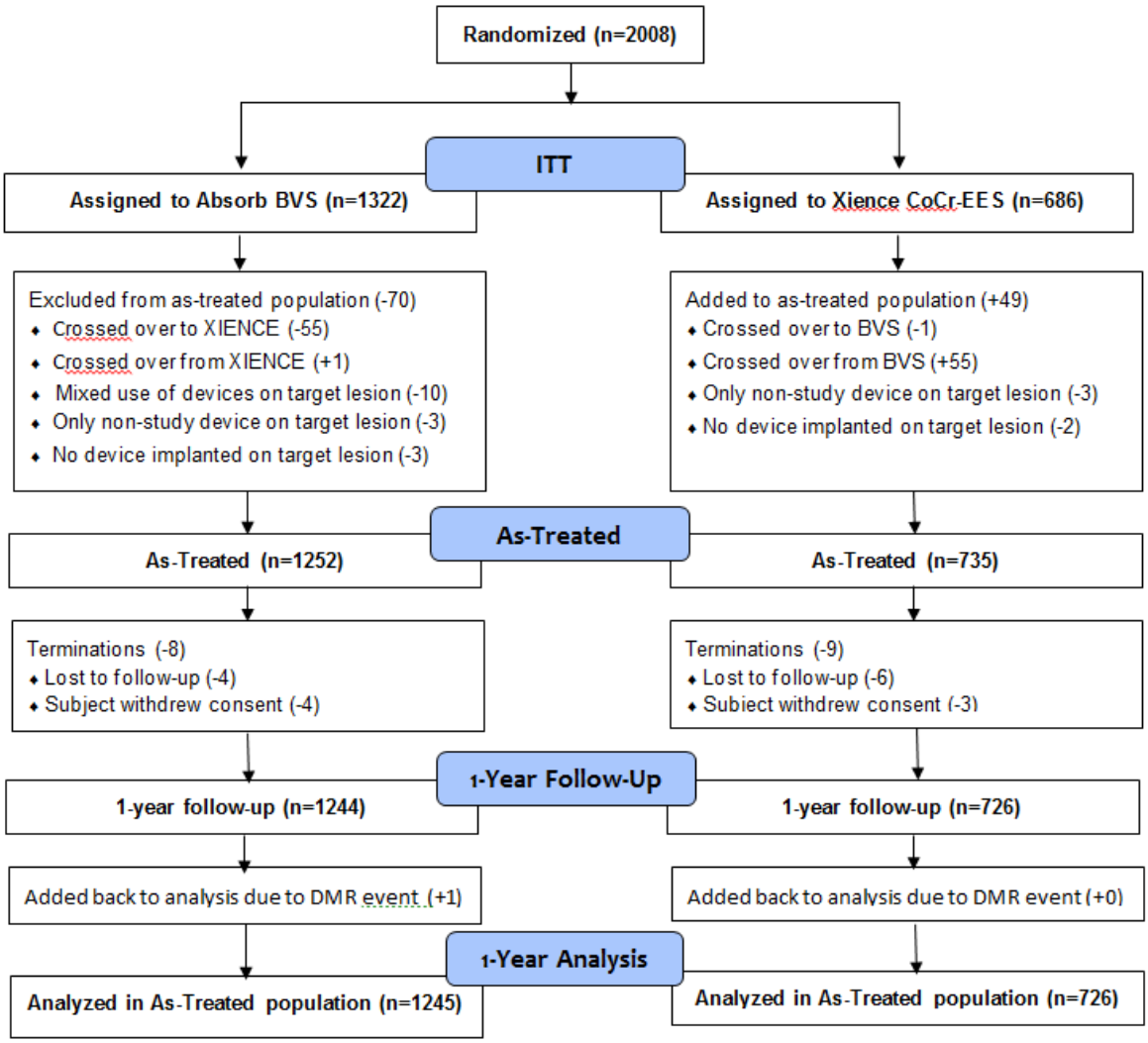


One-year follow-up includes a window of ±28 days.

*Includes 11 subjects who received assigned study device in one lesion but did not receive assigned study device in a second lesion.

**A total of 1312 subjects in the Absorb BVS arm completed 1-year follow-up. However, terminated subjects are included in the ITT (intent-to-treat) analysis population for the 1-year primary endpoint of target lesion failure if they die or have a myocardial infarction or a revascularization event prior to termination. One of the 10 terminated subjects in the Absorb BVS arm fell into this category; thus, there were only 9 Absorb BVS subjects excluded from the analysis, resulting in an actual ITT population of n=1313 in the Absorb BVS arm.

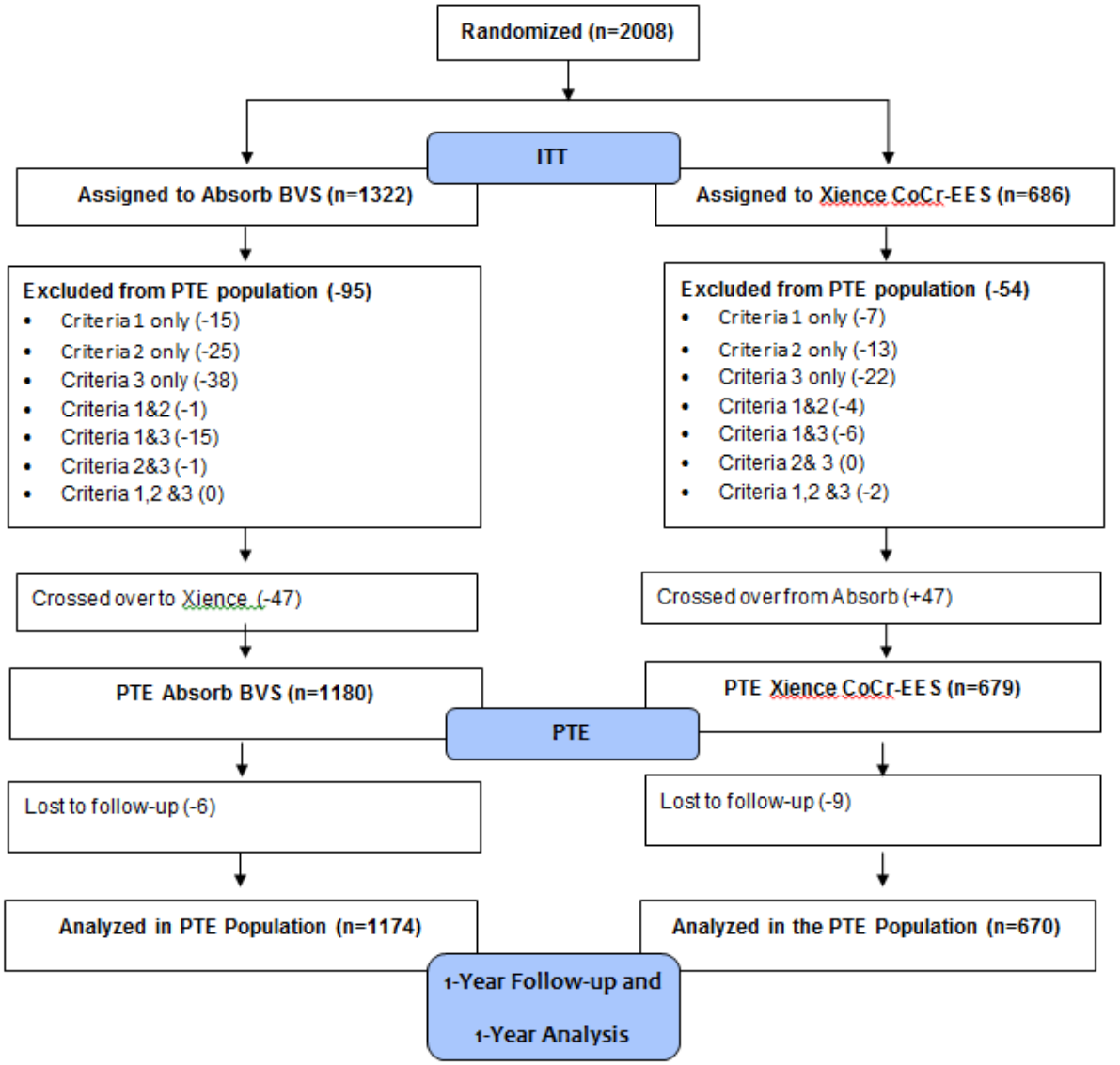
Subject Flow and 1-year follow-up in As-Treated population



Subject Flow and 1-year follow-up in the PTE population

PTE Exclusion Criteria Categorizations

1. Excluded due to angiographic inclusion/exclusion PD
2. Excluded due to general inclusion/exclusion PD
3. Excluded due to treatment strategy PD



C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a PCI study performed in the US.

The key baseline demographic features and risk factors for the ABSORB III ITT population are shown in **Table X-3**. All baseline characteristics were balanced with no statistical differences between the study arms. The mean age was 63.5 ± 10.6 years in the Absorb arm and 63.6 ± 10.3 years in the XIENCE arm. Risk factors having a high prevalence in Absorb and XIENCE arms included hypertension requiring medication

(81.0% (1071/1322) and 80.6% (553/686), respectively) and dyslipidemia requiring medication (76.3% (1009/1322) and 77.7% (533/686), respectively). All diabetes mellitus comprised 31.5% (416/1320) and 32.7% (224/686), respectively, and insulin-required diabetes mellitus subjects comprised 10.5% (138/1320) and 11.2% (77/686), respectively. For cardiac status, the most common disease presentation in Absorb and XIENCE arms was stable angina (57.3% (757/1321) and 60.8% (417/686), respectively). Subjects with a single diseased artery were most prevalent in the ABSORB III population (69.5% (919/1322) and 67.2% (461/686), respectively).

The mean reference vessel diameter was 2.67 ± 0.45 mm and 2.65 ± 0.46 mm in the Absorb and XIENCE groups, respectively. The mean lesion length was 12.6 ± 5.4 mm and 13.1 ± 5.8 mm in the Absorb and XIENCE groups, respectively. The mean diameter stenosis was 65.3% and 65.9% in the Absorb and XIENCE groups, respectively.

Table X-3 ABSORB III Key Baseline Patient Characteristics and Risk Factors – Per-Subject Analysis (Primary Analysis Group, Intent-To-Treat Population)

	Absorb (N=1322)	**XIENCE (N=686)**	**Difference [95% CI][1]**
Subject Background			
Age (year)	63.5 ± 10.6 (1322)	63.6 ± 10.3 (686)	-0.2 [-1.1, 0.8]
Male Subjects	70.7% (934/1322)	70.1% (481/686)	0.53% [-3.62%, 4.80%]
Ethnicity – Hispanic or Latino	3.8% (50/1322)	3.4% (23/686)	0.43% [-1.43%, 2.04%]
Race[2]			
American Indian or Alaskan Native	0.6% (8/1322)	0.3% (2/686)	0.31% [-0.51%, 0.94%]
Asian	1.5% (20/1322)	1.9% (13/686)	-0.38% [-1.81%, 0.75%]
Black or African Heritage	5.3% (70/1322)	5.0% (34/686)	0.34% [-1.84%, 2.27%]
Native Hawaiian or Pacific Islander	0.6% (8/1322)	0.1% (1/686)	0.46% [-0.28%, 1.06%]
White	87.1% (1152/1322)	88.3% (606/686)	-1.20% [-4.11%, 1.92%]
Body Mass Index (kg/m^2)	30.58 ± 6.22 (1322)	30.47 ± 6.26 (686)	0.11 [-0.47, 0.69]
Current Tobacco Use	21.3% (281/1322)	20.7% (142/686)	0.56% [-3.28%, 4.22%]
Any Diabetes Mellitus (DM)	31.5% (416/1320)	32.7% (224/686)	-1.14% [-5.49%, 3.12%]
DM req. Med.	28.2% (372/1320)	28.4% (195/686)	-0.24% [-4.46%, 3.85%]
DM req. Insulin	10.5% (138/1320)	11.2% (77/686)	-0.77% [-3.77%, 2.01%]
HbA1c (%) (All Diabetes Mellitus)	7.56 ± 1.76 (389)	7.78 ± 2.06 (209)	-0.22 [-0.55, 0.11]
Hypertension req. Med.	81.0% (1071/1322)	80.6% (553/686)	0.40% [-3.15%, 4.12%]
Dyslipidemia req. Med.	76.3% (1009/1322)	77.7% (533/686)	-1.37% [-5.16%, 2.57%]
Prior Coronary Intervention	38.7% (512/1322)	38.0% (260/684)	0.72% [-3.79%, 5.16%]
Prior MI	21.5% (282/1311)	22.0% (150/681)	-0.52% [-4.42%, 3.23%]
Cardiac Status			
AMI	2.8% (37/1321)	2.6% (18/686)	0.18% [-1.49%, 1.59%]

	Absorb	XIENCE	Difference
Unstable Angina	26.9% (355/1321)	24.5% (168/686)	2.38% [-1.70%, 6.31%]
Stable Angina	57.3% (757/1321)	60.8% (417/686)	-3.48% [-7.96%, 1.07%]
Silent Ischemia	10.0% (132/1321)	10.2% (70/686)	-0.21% [-3.12%, 2.47%]
No Current Evidence of Ischemia	2.1% (28/1321)	1.3% (9/686)	0.81% [-0.52%, 1.92%]
Single diseased artery	69.5% (919/1322)	67.2% (461/686)	2.31% [-1.93%, 6.65%]
Two diseased arteries	24.3% (321/1322)	26.4% (181/686)	-2.10% [-6.19%, 1.85%]
Three or more diseased arteries	6.2% (82/1322)	6.4% (44/686)	-0.21% [-2.61%, 1.94%]

[1]By normal approximation for continuous variables and Newcombe score method for binary variables.
[2]Subject can be counted in more than one category

D. Safety and Effectiveness Results

The primary endpoint of TLF at 1 year was in the ITT population was met and is shown below in **Table X-4**. The TLF rate at 1 year was 7.8% (102/1313) in the Absorb arm and 6.1% (41/677) in the XIENCE arm. The difference between the two treatment arms was 1.71% with the upper bound of the 95% confidence interval being 3.93%, which was less than the non-inferiority margin of 4.5%. The Absorb arm was non-inferior to XIENCE with a non-inferiority p-value of 0.0070 for observed TLF rates at 1 year.

Table X-4 ABSORB III Primary Endpoint Analysis (Primary Analysis Group - Intent-to-Treat Population, Per-Protocol MI Definition)

	Absorb (N=1322)	XIENCE (N=686)	Difference (95% CI[1])	Non-Inferiority P-Value[2]
1-Year TLF (Cardiac Death Target Vessel MI, ID-TLR[3])	7.8% (102/1313)	6.1% (41/677)	1.71% (-0.51%, 3.93%)	0.0070

[1]Two-sided 95% confidence interval by Farrington-Manning method
[2]One-sided p-value by using Farrington-Manning non-inferiority test statistic with non-inferiority margin of 4.5%, to be compared with a one-sided significance level of 0.025
[3]Ischemia-driven target lesion revascularization
Note: 1-year timeframe includes a window of ± 28 days
Note: N is the total number of subjects
Note: MI is per protocol definition: Non Q-wave MI is defined as CK-MB > 5X ULN for peri-procedural MI (≤ 48 hrs post-PCI); CK-MB or Troponin > ULN plus evidence of ischemia for spontaneous MI; Q-wave MI defined as development of new, pathological Q wave on the ECG

For the PTE population, the TLF rate at 1 year was 7.8% (91/1174) in the Absorb arm and 5.7% (38/670) in the XIENCE arm. The difference between the two treatment arms was 2.08% with the upper bound of the 95% confidence interval being 4.35%, which was less than the non-inferiority margin of 4.5%. The Absorb arm was non-inferior to XIENCE regarding the primary endpoint TLF rate at 1 year in the PTE population (p = 0.0183).

The analyses of Angina, All Revascularization, and ID-TVR at 1 year for the ITT population are shown in **Table X-5**. Superiority was not met for any of the powered secondary endpoints with pre-specified hypothesis tests. The Angina rate at 1 year was 18.3% (238/1303) in the Absorb arm and 18.4% (125/678) in the XIENCE arm (p = 0.9256). The All Revascularization rate at 1 year was 9.1% (120/1313) in the Absorb arm and 8.1% (55/677) in the XIENCE arm. The ID-TVR rate at 1 year was 5.0% (66/1313) in the Absorb arm and 3.7% (25/677) in the XIENCE arm.

Table X-5 ABSORB-III Powered Secondary Endpoints (Primary Analysis Group - Intent-to-Treat Population)

Powered Secondary Endpoints	Absorb (N=1322)	XIENCE (N=686)	Difference [95% CL][4]	Superiority P-Value[5]
1-Year Angina[1]	18.3% (238/1303)	18.4% (125/678)	-0.17% [-3.77%, 3.42%]	0.9256
1-Year All Revascularization[2]	9.1% (120/1313)	8.1% (55/677)	1.02% [-1.57%, 3.60%]	N/A[6]
1-Year ID-TVR[3]	5.0% (66/1313)	3.7% (25/677)	1.33% [-0.51%, 3.18%]	N/A[6]

[1]First reported angina post discharge (excluding angina following the index procedure through discharge, not to exceed a period of 7 days).
[2]Includes TLR, TVR non TLR, and non TVR
[3]Ischemia driven target vessel revascularization
[4]Without multiplicity adjustment. For Angina at 1 year, Pearson's Chi-square two-sided 95% confidence interval. For All Revascularization and ID-TVR at 1 year, exact two-sided 95% confidence interval.
[5]Compared with a two-sided significance level of 0.05. For Angina at 1 year, two-sided p-value using Pearson's Chi-square test statistic. For All Revascularization and ID-TVR at 1 year, two-sided p-value using Fisher's exact test statistic.
[6]According to the pre-specified testing sequence, further testing stopped after the superiority hypothesis test of 1-year angina was not passed. The superiority hypothesis tests of 1-year all revascularization and 1-year ID-TVR were not passed.
Note: 1-year timeframe includes a window of ± 28 days
Note: N is the total number of subjects

The safety and effectiveness results are presented in **Table X-6**.

Table X-6 ABSORB-III Clinical Results (Primary Analysis Group – Intent-to-Treat Population)

	Absorb (N = 1322)	**XIENCE (N = 686)**
IN-HOSPITAL OUTCOMES		
TLF (COMPOSITE OF SAFETY AND EFFECTIVENESS)	3.3% (43/1319)	3.1% (21/686)
EFFECTIVENESS		
Ischemia-Driven TLR	0.3% (4/1319)	0.6% (4/686)
TLR, CABG	0.0% (0/1319)	0.1% (1/686)
TLR, PCI	0.3% (4/1319)	0.6% (4/686)
Ischemia-Driven TVR	0.4% (5/1319)	0.6% (4/686)
SAFETY		
All Death	0.1% (1/1319)	0.0% (0/686)
Cardiac Death	0.1% (1/1319)	0.0% (0/686)
Vascular Death	0.0% (0/1319)	0.0% (0/686)
Non-cardiovascular Death	0.0% (0/1319)	0.0% (0/686)
All MI	3.0% (40/1319)	3.1% (21/686)
TV-MI	3.0% (39/1319)	2.9% (20/686)
QMI	0.1% (1/1319)	0.3% (2/686)
NQMI	2.9% (38/1319)	2.6% (18/686)
NTV-MI	0.1% (1/1319)	0.1% (1/686)
QMI	0.0% (0/1319)	0.0% (0/686)
NQMI	0.1% (1/1319)	0.1% (1/686)
Cardiac Death or MI	3.1% (41/1319)	3.1% (21/686)
30-DAY OUTCOMES		
MACE	4.9% (65/1317)	3.6% (25/686)

Note: 1-year timeframe includes a window of ± 28 days

Note: N is the total number of subjects

Note: MI is per protocol definition: Non Q-wave MI is defined as CK-MB > 5X ULN for peri-procedural MI (≤ 48 hrs post-PCI); CK-MB or Troponin > ULN plus evidence of ischemia for spontaneous MI; Q-wave MI defined as development of new, pathological Q wave on the ECG;

Note: Major Adverse Cardiac Events (MACE) is the composite of cardiac death, all MI and ID-TLR

Table X-6 ABSORB-III Clinical Results (Primary Analysis Group – Intent-to-Treat Population) (continued)

	Absorb (N=1322)	**XIENCE (N=686)**
1-YEAR OUTCOMES		
TLF (COMPOSITE OF SAFETY AND EFFECTIVENESS)	7.8% (102/1313)	6.1% (41/677)
EFFECTIVENESS		
Ischemia-Driven TLR	3.0% (40/1313)	2.5% (17/677)
TLR, CABG	0.2% (3/1313)	0.4% (3/677)
TLR, PCI	2.8% (37/1313)	2.2% (15/677)
Ischemia-Driven TVR	5.0% (66/1313)	3.7% (25/677)
SAFETY		
All Death	1.1% (15/1313)	0.4% (3/677)
Cardiac Death	0.6% (8/1313)	0.1% (1/677)
Vascular Death	0.2% (2/1313)	0.0% (0/677)
Non-cardiovascular Death	0.4% (5/1313)	0.3% (2/677)
All MI (Per Protocol Definition)	6.9% (90/1313)	5.6% (38/677)
TV-MI	6.0% (79/1313)	4.6% (31/677)
QMI	0.7% (9/1313)	0.3% (2/677)
NQMI	5.3% (70/1313)	4.3% (29/677)
NTV-MI	0.8% (11/1313)	1.2% (8/677)
QMI	0.1% (1/1313)	0.1% (1/677)
NQMI	0.8% (10/1313)	1.0% (7/677)
Cardiac Death or MI	7.5% (98/1313)	5.8% (39/677)
Cumulative ARC-defined Definite + Probable Stent/Scaffold Thrombosis (0-393 days)	1.54% (20/1301)	0.74% (5/675)
Acute (≤ 1 day)	0.15% (2/1320)	0.58% (4/686)
Sub-Acute (> 1-30 days)	0.91% (12/1315)	0.15% (1/686)

	Absorb (N=1322)	XIENCE (N=686)
Late (31-365 days)	0.46% (6/1299)	0.00% (0/675)
Very Late (> 365-393 days)	0.00% (0/1299)	0.00% (0/675)

Note: 1-year timeframe includes a window of ± 28 days
Note: N is the total number of subjects
Note: MI is per protocol definition: Non Q-wave MI is defined as CK-MB > 5X ULN for peri-procedural MI (≤ 48 hrs post-PCI); CK-MB or Troponin > ULN plus evidence of ischemia for spontaneous MI; Q-wave MI defined as development of new, pathological Q wave on the ECG

1. Safety Results

The analysis of safety was based on the primary analysis cohort of 1,990 patients with available data for the 12-month evaluation at the time of the database lock.

The key cardiovascular safety outcomes for this study (death, MI and stent/scaffold thrombosis) are presented above in **Table X-4** and **Table X-6**. TLF is a composite of safety and effectiveness events. For nearly all cardiovascular safety endpoints evaluated in-hospital, at 30-days and at 1-year, Absorb had slightly higher observed rates compared to XIENCE, but the differences between the treatment groups were not statistically significant.

Adverse events reported for all randomized subjects are shown in **Table X-7 (Absorb arm)** and **Table X-8 (XIENCE arm)**.

Table X-7 Non-Hierarchical Subject Counts of Site Reported Adverse Events by MedDRA Code through 1 Year (ABSORB III Primary Analysis Group) (Intent-to-Treat Population) (Absorb BVS Subgroup)

System Organ Class Preferred Term	Total (N=1322)	Device or Procedure-Related (N=1322)	SAE (N=1322)
Blood and lymphatic system disorders	2.0% (26/1322)	0.3% (4/1322)	0.4% (5/1322)
Cardiac disorders	35.1% (464/1322)	18.2% (241/1322)	16.8% (222/1322)
Congenital, familial and genetic disorders	0.2% (2/1322)	0.0% (0/1322)	0.0% (0/1322)
Ear and labyrinth disorders	0.8% (11/1322)	0.0% (0/1322)	0.1% (1/1322)
	0.5%	0.0%	0.0%

Table X-7 Non-Hierarchical Subject Counts of Site Reported Adverse Events by MedDRA Code through 1 Year (ABSORB III Primary Analysis Group) (Intent-to-Treat Population) (Absorb BVS Subgroup)

System Organ Class Preferred Term	Total (N=1322)	Device or Procedure-Related (N=1322)	SAE (N=1322)
Endocrine disorders	(7/1322)	(0/1322)	(0/1322)
Eye disorders	1.7% (23/1322)	0.1% (1/1322)	0.2% (3/1322)
Gastrointestinal disorders	10.7% (142/1322)	0.6% (8/1322)	1.9% (25/1322)
General disorders and administration site conditions	29.7% (393/1322)	10.8% (143/1322)	4.3% (57/1322)
Hepatobiliary disorders	0.8% (11/1322)	0.0% (0/1322)	0.5% (6/1322)
Immune system disorders	0.8% (11/1322)	0.2% (2/1322)	0.1% (1/1322)
Infections and infestations	11.1% (147/1322)	0.4% (5/1322)	2.7% (36/1322)
Injury, poisoning and procedural complications	12.5% (165/1322)	4.4% (58/1322)	3.8% (50/1322)
Investigations	28.3% (374/1322)	21.6% (285/1322)	0.9% (12/1322)
Metabolism and nutrition disorders	4.4% (58/1322)	0.2% (3/1322)	0.8% (11/1322)
Musculoskeletal and connective tissue disorders	12.3% (162/1322)	1.1% (15/1322)	1.1% (14/1322)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2.3% (30/1322)	0.0% (0/1322)	1.1% (15/1322)
Nervous system disorders	12.6% (167/1322)	0.8% (11/1322)	3.3% (43/1322)
Psychiatric disorders	2.9% (38/1322)	0.1% (1/1322)	0.2% (2/1322)
Renal and urinary disorders	3.5% (46/1322)	0.2% (2/1322)	0.6% (8/1322)
	1.7%	0.2%	0.2%

Table X-7 Non-Hierarchical Subject Counts of Site Reported Adverse Events by MedDRA Code through 1 Year (ABSORB III Primary Analysis Group) (Intent-to-Treat Population) (Absorb BVS Subgroup)

System Organ Class Preferred Term	Total (N=1322)	Device or Procedure-Related (N=1322)	SAE (N=1322)
Reproductive system and breast disorders	(23/1322)	(2/1322)	(3/1322)
Respiratory, thoracic and mediastinal disorders	14.0% (185/1322)	0.8% (11/1322)	2.9% (38/1322)
Skin and subcutaneous tissue disorders	4.2% (55/1322)	0.4% (5/1322)	0.2% (2/1322)
Surgical and medical procedures	0.5% (6/1322)	0.0% (0/1322)	0.2% (3/1322)
Vascular disorders	9.8% (130/1322)	1.2% (16/1322)	2.3% (30/1322)

Table X-8 Non-Hierarchical Subject Counts of Site Reported Adverse Events by MedDRA Code through 1 Year (ABSORB III Primary Analysis Group) (Intent-to-Treat Population) (XIENCE Subgroup)

System Organ Class Preferred Term	Total (N=686)	Device or Procedure-Related (N=686)	SAE (N=686)
Blood and lymphatic system disorders	1.6% (11/686)	0.1% (1/686)	0.6% (4/686)
Cardiac disorders	35.7% (245/686)	16.9% (116/686)	14.4% (99/686)
Congenital, familial and genetic disorders	0.1% (1/686)	0.0% (0/686)	0.0% (0/686)
Ear and labyrinth disorders	1.0% (7/686)	0.0% (0/686)	0.1% (1/686)
Endocrine disorders	0.3% (2/686)	0.0% (0/686)	0.0% (0/686)
Eye disorders	1.5% (10/686)	0.1% (1/686)	0.6% (4/686)
Gastrointestinal disorders	11.4% (78/686)	1.0% (7/686)	2.2% (15/686)
General disorders and administration site	29.0% (199/686)	9.8% (67/686)	5.1% (35/686)

Table X-8 Non-Hierarchical Subject Counts of Site Reported Adverse Events by MedDRA Code through 1 Year (ABSORB III Primary Analysis Group) (Intent-to-Treat Population) (XIENCE Subgroup)

System Organ Class Preferred Term	Total (N=686)	Device or Procedure-Related (N=686)	SAE (N=686)
conditions			
Hepatobiliary disorders	1.3% (9/686)	0.0% (0/686)	0.7% (5/686)
Immune system disorders	1.3% (9/686)	0.1% (1/686)	0.0% (0/686)
Infections and infestations	12.8% (88/686)	0.0% (0/686)	4.1% (28/686)
Injury, poisoning and procedural complications	14.3% (98/686)	5.2% (36/686)	3.4% (23/686)
Investigations	25.7% (176/686)	18.8% (129/686)	0.7% (5/686)
Metabolism and nutrition disorders	3.4% (23/686)	0.4% (3/686)	0.6% (4/686)
Musculoskeletal and connective tissue disorders	12.2% (84/686)	1.6% (11/686)	1.6% (11/686)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3.2% (22/686)	0.0% (0/686)	0.6% (4/686)
Nervous system disorders	10.6% (73/686)	0.9% (6/686)	2.0% (14/686)
Psychiatric disorders	2.6% (18/686)	0.0% (0/686)	0.6% (4/686)
Renal and urinary disorders	4.2% (29/686)	0.4% (3/686)	1.3% (9/686)
Reproductive system and breast disorders	0.7% (5/686)	0.0% (0/686)	0.0% (0/686)
Respiratory, thoracic and mediastinal disorders	13.0% (89/686)	0.9% (6/686)	1.3% (9/686)
Skin and subcutaneous tissue disorders	2.6% (18/686)	0.3% (2/686)	0.0% (0/686)
Surgical and medical procedures	0.7% (5/686)	0.0% (0/686)	0.4% (3/686)

Table X-8 Non-Hierarchical Subject Counts of Site Reported Adverse Events by MedDRA Code through 1 Year (ABSORB III Primary Analysis Group) (Intent-to-Treat Population) (XIENCE Subgroup)

System Organ Class Preferred Term	Total (N=686)	Device or Procedure-Related (N=686)	SAE (N=686)
Vascular disorders	8.5% (58/686)	1.3% (9/686)	3.1% (21/686)

Adverse Effects that Occurred in the PMA Clinical Study:

The incidence rate and number of all adverse events (AEs) were tabulated in MedDRA system organ class (SOC). Device or procedural relationship as was determined by the trial investigator, including those were deemed "possible" or "unknown" and whether or not the serious adverse event (SAE) criteria was met. Overall, the incidence rates of AEs were comparable between the treatment (Absorb) and control (XIENCE) groups. As expected in this patient population, the highest frequency occurred in SOC "cardiac disorders," which reflects the underlying condition, "general disorders and administrative site condition" and "injury, poisoning, and procedural complication," both of which represents procedure-related AEs common to all invasive procedures, and "investigations," most of which consist of post-procedural abnormalities in cardiac enzymes/biomarkers and ECGs. The distribution for procedural or device relationship and SAE criteria for these AEs were comparable between the Absorb and XIENCE groups.

2. Effectiveness Results

The analysis of effectiveness was based on the 1,990 evaluable patients at the 12-month time point. Key effectiveness outcomes are presented in Tables X-4 and X-5. The 1-year primary endpoint of TLF is a composite of safety and effectiveness endpoints. The key effectiveness outcomes were Angina, All Revascularization, ID-TVR and ID-TLR at 1 year. Absorb failed to meet superiority for the endpoint of angina at 1-year, all revascularization at 1-year, and ID-TVR at 1-year vs. XIENCE (**Table X-5**). However, Absorb was comparable to XIENCE for all key effectiveness endpoints (**Table X-6**).

3. Subgroup Analyses

The following pre-index procedure characteristics were evaluated for potential association with outcomes: age, gender, reference vessel diameter and diabetes. Subgroup analyses of the primary endpoint showed similar clinical outcomes with no statistical differences in 1-year TLF between the Absorb and XIENCE arms for all pre-specified subgroups.

Analysis by Age

The ABSORB III trial had a median subject age of 64 years, with no upper age limit. The assessment of geriatric effect in the ABSORB III trial for the primary endpoint of TLF at 1 year showed no significant treatment interaction by age ≥ median and age < median (p = 0.6924). The safety and effectiveness of Absorb GT1 BVS in pediatric subjects have not been established.

Analysis Stratified by Gender

A subgroup analysis by gender was conducted. Female patients represented 29.5% (593/2008) of the randomized trial population. The 1-year rates of TLF, non-hierarchically assessed cardiac death, TV-MI and ID-TLR, and stent / scaffold thrombosis for the overall population, female subgroup, and male subgroup are shown in **Table X-9**. Compared to the overall population, females had slightly higher TLF rates for both device arms, which were mainly driven by numerically higher rates of TV-MI. The observed differences in TLF and component endpoint rates between the two device arms within each gender group are comparable. The difference in scaffold thrombosis rates between the two treatment groups was numerically lower for females compared to males, primarily due to a disproportionally low stent thrombosis rate in male subjects treated with XIENCE.

Table X-9 Subgroup Information and 1-Year Clinical Outcomes Stratified by Gender – Per-Subject Analysis (Primary Analysis Group, Intent-to-Treat Population, Per Protocol MI Definition)

	Overall ITT Population		**Female**		**Male**	
	Absorb (N=1322)	**XIENCE (N=686)**	**Absorb (N=388)**	**XIENCE (N=205)**	**Absorb (N=934)**	**XIENCE (N=481)**
TLF	7.8% (102/1313)	6.1% (41/677)	8.5% (33/386)	7.4% (15/203)	7.4% (69/927)	5.5% (26/474)
Cardiac Death	0.6% (8/1313)	0.1% (1/677)	0.3% (1/386)	0.0% (0/203)	0.8% (7/927)	0.2% (1/474)
TV- MI	6.0% (79/1313)	4.6% (31/677)	7.3% (28/386)	5.4% (11/203)	5.5% (51/927)	4.2% (20/474)
ID-TLR	3.0% (40/1313)	2.5% (17/677)	3.4% (13/386)	3.9% (8/203)	2.9% (27/927)	1.9% (9/474)
Stent / Scaffold Thrombosis (Def / Prob)	1.54% (20/1301)	0.74% (5/675)	1.56% (6/384)	1.97% (4/203)	1.53% (14/917)	0.21% (1/472)

Note: N is the total number of subjects
Note: MI is per protocol definition

Implantation of Absorb in Small Coronary Arteries (Post Hoc Analysis)

In the ABSORB III trial, the target vessel size inclusion criterion was a reference vessel diameter (RVD) determined following pre-dilatation of ≥ 2.5 mm to ≤ 3.75 mm by visual estimation by the operator. In the overall ABSORB III population, 19% (375/1998) of subjects had an RVD < 2.25 mm as assessed by quantitative coronary angiography (QCA), and 81% (1623/1998) had a RVD ≥ 2.25 mm (by QCA).

Table X-10 shows the results of a post hoc analysis of the key clinical results stratified by the QCA-assessed RVD subgroups of ≥ 2.25 mm and < 2.25 mm. The 2.25 mm QCA threshold was chosen because visual estimates of coronary artery dimensions typically overestimate true vessel diameters as measured by QCA by approximately 0.25 mm.

In the RVD < 2.25 mm (by QCA) subgroup, the observed TLF rate at 1-year was 12.9% for Absorb and 8.3% for XIENCE. The difference in the TLF rate was primarily driven by a higher observed rate of target vessel MI in the Absorb group. In this small vessel subgroup, the observed definite plus probable scaffold/stent thrombosis rate at 1-year was 4.6% in Absorb vs. 1.5% in XIENCE.

In the RVD ≥ 2.25 mm (by QCA) subgroup, the observed TLF rate at 1-year was 6.7% for Absorb vs. 5.5% for XIENCE. In this subgroup, the observed definite plus probable scaffold/stent thrombosis rate at 1-year was 0.9% in Absorb vs. 0.6% in XIENCE.

Table X-10 Clinical Results for ABSORB III Stratified by Pre-Procedure RVD Size – QCA-Assessed RVD ≥ 2.25 mm and RVD < 2.25 mm by QCA (ITT population) Procedure RVD Size

	Subjects with QCA-Assessed RVD ≥ 2.25 mm		**Subjects with QCA-Assessed RVD < 2.25 mm***	
	Absorb (N=1074)	**XIENCE (N=549)**	**Absorb (N=242)**	**XIENCE (N=133)**
Percentage of Subjects	81.6% (1074/1316)	80.5% (549/682)	18.4% (242/1316)	19.5% (133/682)
Pre-procedure Median RVD by QCA (mm) Range (min, max)	2.75 (2.25, 4.04)	2.72 (2.26, 4.48)	2.08 (1.39, 3.54)	2.10 (1.46, 3.49)
TLF	6.7% (71/1067)	5.5% (30/542)	12.9% (31/241)	8.3% (11/133)
Cardiac Death	0.6% (6/1067)	0.2% (1/542)	0.8% (2/241)	0.0% (0/133)
TV- MI	5.2% (55/1067)	4.6% (25/542)	10.0% (24/241)	4.5% (6/133)

	Subjects with QCA-Assessed RVD ≥ 2.25 mm		Subjects with QCA-Assessed RVD < 2.25 mm*	
	Absorb (N=1074)	**XIENCE (N=549)**	**Absorb (N=242)**	**XIENCE (N=133)**
ID-TLR	2.2% (24/1067)	1.5% (8/542)	6.6% (16/241)	6.8% (9/133)
Stent/Scaffold Thrombosis (Def/Prob)	0.9% (9/1058)	0.6% (3/540)	4.6% (11/238)	1.5% (2/133)

Note: N is the total number of subjects

Note: MI is per protocol definition

*The ITT subjects with at least one target lesion pre-procedure RVD < 2.25 mm (core-lab measurement) are included in the analysis.

Analysis of Diabetic Subjects in ABSORB III

Patients with diabetes mellitus are at increased risk for cardiovascular morbidity and mortality and are associated with worse clinical outcomes when undergoing PCI compared with non-diabetics. In the ABSORB III trial, diabetic patients represented 31.9% (640/2006) of the overall trial population. The 1-year rates of TLF, non-hierarchically assessed cardiac death, TV-MI and ID-TLR, and stent/scaffold thrombosis for the overall population, the all diabetes mellitus (all DM) subgroup, and the all non-DM subgroup are shown in **Table X-11**.

For the all DM subgroup, the observed clinical event rates in both the Absorb and XIENCE arms were higher than in the overall ABSORB III ITT population and the non-DM subgroup for most key outcome measures. For most endpoints, the event rate difference between ABSORB and XIENCE in the overall ABSORB III ITT population was similar to the event rate difference between treatment groups in the all DM subgroup and in the all non-DM subgroup.

Table X-11 Subgroup Information and 1-Year Clinical Outcomes Stratified by Diabetic Status – Per-Subject Analysis (Primary Analysis Group, Intent-to-Treat Population, Per Protocol MI Definition)

	Overall ITT Population		All DM		All Non-DM	
	Absorb (N=1322)	**XIENCE (N=686)**	**Absorb (N=416)**	**XIENCE (N=224)**	**Absorb (N=904)**	**XIENCE (N=462)**
TLF	7.8% (102/1313)	6.1% (41/677)	10.7% (44/411)	9.1% (20/220)	6.3% (57/900)	4.6% (21/457)
Cardiac Death	0.6% (8/1313)	0.1% (1/677)	0.5% (2/411)	0.0% (0/220)	0.7% (6/900)	0.2% (1/457)

	Overall ITT Population		All DM		All Non-DM	
	Absorb (N=1322)	**XIENCE (N=686)**	**Absorb (N=416)**	**XIENCE (N=224)**	**Absorb (N=904)**	**XIENCE (N=462)**
TV- MI	6.0% (79/1313)	4.6% (31/677)	9.0% (37/411)	7.3% (16/220)	4.6% (41/900)	3.3% (15/457)
ID-TLR	3.0% (40/1313)	2.5% (17/677)	5.6% (23/411)	3.6% (8/220)	1.8% (16/900)	2.0% (9/457)
Stent / Scaffold Thrombosis (Def / Prob)	1.54% (20/1301)	0.74% (5/675)	3.2% (13/405)	1.4% (3/219)	0.8% (7/894)	0.4% (2/456)

Note: N is the total number of subjects
Note: MI is per protocol definition

The ABSORB III trial showed a more pronounced risk of TLF (primarily driven by an observed increased rate of target vessel MI) and definite plus probable scaffold/stent thrombosis at 1-year in diabetic patients with an RVD < 2.25 mm (by QCA) treated with Absorb compared with treatment with XIENCE. These data must be viewed with caution given the small sample size of this analysis.

4. Pharmacokinetics – ABSORB III PK

Study Design

ABSORB III PK is a sub-study of ABSORB III with the objective of determining the pharmacokinetics of everolimus delivered by the Absorb scaffold in a cohort of 12 subjects (at 2 US clinical sites) who received only Absorb to treat a maximum of two *de novo* coronary lesions.

Subjects had to meet the inclusion and exclusion criteria of the ABSORB III clinical trial but were not permitted to undergo PCI of non-target lesions.

Arterial or venous blood was scheduled to be drawn at baseline (prior to placement of the first Absorb), at 10, 30 minutes, and at 1, 2, 4, 6, 12, 24, 48, 72, 96, 120, 168, 336 and 720 hours (30 days) post-Absorb implantation. All PK subjects will be clinically followed through 5 years, with visits at 30 and 180 days, and at 1, 2, 3, 4 and 5 years.

Whole blood samples were temporarily stored at -70°C at the investigational site and were shipped to a central core laboratory. The concentration of everolimus in whole blood samples was determined by a validated Liquid Chromatography-Mass Spectrometry/ Mass Spectrometry (LC-MS/MS) assay in the bioanalytical core laboratory. The lower limit of quantification (LLOQ) of everolimus in the blood samples was 0.1 ng/mL. Pharmacokinetic analysis of the everolimus blood concentration-time data was conducted by the pharmacokinetics core laboratory using

non-compartmental methods. The following parameters were calculated: C_{max}, t_{max}, AUC_{24h}, AUC_{last}, $AUC_{0-\infty}$, λz, $t_{1/2}$, CL:

C_{max} (ng/mL)	Maximal observed blood everolimus concentration
t_{max} (h)	Time to reach the maximal observed blood everolimus concentration
AUC_{24h} (ng.h/mL)	Area under the blood everolimus concentration vs. time curve from time 0 up to 24 hours post placement of the last Absorb, calculated by the linear up/log down trapezoidal method
AUC_{last} (ng.h/mL)	Area under the blood everolimus concentration vs. time curve from time 0 up to the last quantifiable concentration, calculated by the linear up/log down trapezoidal method
$AUC_{0-\infty}$ (ng.h/mL)	Area under the blood everolimus concentration vs. time curve from time zero and extrapolated to infinite time, calculated as: $AUC_{0-\infty} = AUC_{last} + (C_{last}/\lambda z)$ The percentage of $AUC_{0-\infty}$ obtained by extrapolation ($\%AUC_{0-\infty ex}$) is calculated as: $\%AUC_{0-\infty ex} = 100*(AUC_{0-\infty} - AUC_{last})/ AUC_{0-\infty}$
λz (1/h)	Terminal rate constant, determined by linear regression of terminal points of the ln-linear analyte concentration-time curve
$t_{1/2}$ (h)	Terminal half-life, calculated as $t_{1/2} = 0.693/\lambda z$
CL (L/h)	Clearance, calculated as Dose/AUC0-∞

Whole blood concentration-time data were listed by nominal sampling time. If an actual sampling time deviated by 20% or more from the scheduled time, this sample was excluded from descriptive statistics in the blood concentration-time table. Summary statistics include sample size (N), mean, standard deviation (SD), percentage of coefficient of variation (%CV), geometric mean, median, minimum, and maximum. To explore dose proportionality of everolimus, a regression analysis on dose-normalized (to 1 μg) PK parameters (C_{max}, AUC_{24h}, AUC_{last}, and $AUC_{0-\infty}$) for everolimus was performed using the regression procedure (PROC REG) in SAS.

Accountability of Subjects

The first subject was registered on June 2, 2014 and the last subject was registered on September 17, 2014. There was no early subject termination from the study at or before the 30-day follow-up visit.

Study Population Demographics and Baseline Parameters

The characteristics of the PK sub-study participants are similar to the characteristics of the ABSORB III primary analysis group. The PK patient population consisted of predominantly males (91.7%) with a mean age of 60.1± 10.5 years. There was a high prevalence of hypertension (100%) and dyslipidemia (100%). Over 30% (33.3%) of subjects were diabetic. All patients had a single *de novo* target lesion in a native coronary artery.

Results

The pharmacokinetics (PK) of everolimus eluted from the Absorb scaffold was evaluated in all 12 subjects. Four subjects received two Absorb and eight subjects received one Absorb, with the diameters of 2.5, 3.0, and 3.5 mm and lengths of 8, 12, 18, and 28 mm. The total everolimus dose ranged from 181 to 443 µg.

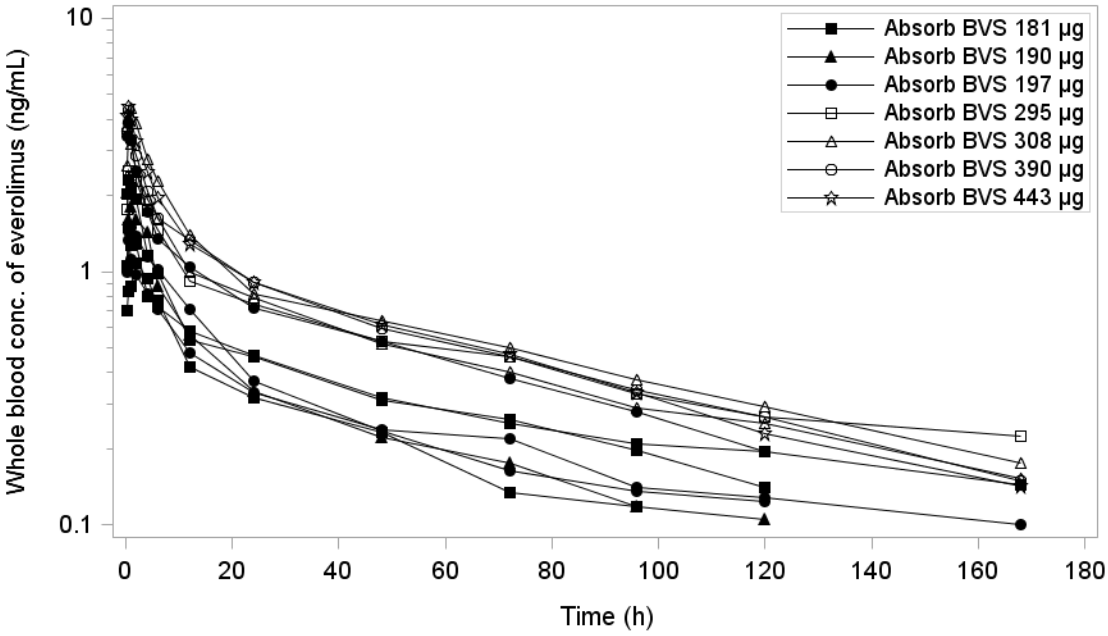
The results of the ABSORB III PK sub-study are presented in **Figure X-1** (everolimus blood concentration-time curve) and **Table X-12** (everolimus PK parameters). Everolimus concentrations increased rapidly after the scaffold deployment, reaching maximum concentrations between 0.17 and 2.37 hours (t_{max}). The everolimus concentrations declined thereafter with a terminal half-life ranging between 45.9 and 115 hours. Everolimus concentrations were low but measurable up to 168 hours (7 days) after last scaffold deployment.

The maximum observed everolimus concentration (C_{max}) values increased with dose and ranged from 1.085 to 4.460 ng/mL across the dosage range studied. Similarly, individual AUC24h (ranging from 12.09 to 44.22 ng.h/mL), AUClast (ranging from 25.37 to 104.6 ng.h/mL) and AUC0-∞ (ranging from 33.15 to 120.8 ng.h/mL) increased proportionally with dose. Further, dose-normalized C_{max} and area under the concentration-time curve (AUC[a]) were comparable across the total scaffold dose, indicating that the systemic exposure increased proportionally with the total scaffold dose. Overall, inter-subject variability was acceptable[b]: 23.3% and 35.6% for dose-normalized AUC0-∞ and C_{max}, respectively.

The results of the PK study are consistent with previous clinical studies using the XIENCE V stent and are in accordance with the preclinical profile of everolimus. Individual C_{max} values (1.085 to 4.460 ng/mL) were slightly higher than the minimum systemic therapeutic level of 3.0 ng/mL necessary to be maintained for effective prevention of organ rejection[1,2]. However, as opposed to a chronic systemic therapy, everolimus blood concentrations decline rapidly after Absorb implantation. By 4 hours after the last scaffold deployment, blood concentrations were below 3.0 ng/mL (the chronically maintained therapeutic level necessary for effective organ rejection prevention) in all subjects. The rapid disappearance of everolimus from the circulation after implantation of Absorb, limits the extent of systemic exposure, and is therefore considered safe.

[a] AUC_{24h}: from time 0 to 24 hours; AUC_{last}: from time 0 up to the last quantifiable concentration; $AUC_{0-\infty}$: from time zero and extrapolated to infinite time

[b] Inter-subject variability was considered acceptable based on an inter-subject variability > 30% is considered very high.



Note: 181 µg (n=3 subjects); 190 µg (n=1 subject); 197 µg (n=3 subjects); 295 µg (n=1 subject); 308 µg (n=2 subjects); 390 µg (n=1 subject); 443 µg (n=1 subject).

Figure X-1 ABSORB III PK - Combined Whole Blood Concentration-Time Curves of Everolimus

Table X-12 ABSORB III PK -Whole Blood Pharmacokinetic Parameters in Subjects Following Absorb Implantation

Dose Range (µg)	**t_{max} (h)**	**C_{max} (ng/mL)**	**$t_{1/2term}$ (h)**	**AUC_{24h} h.ng/mL**	**AUC_{last} h.ng/mL**	**$AUC_{0-\infty}$ h.ng/mL**	**CL (L/h)**
	Median (range)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
181 - 443	0.55 (0.17-2.37)	2.74 ± 1.308	67.20 ± 18.8	24.84 ± 11.04	61.88 ± 28.41	76.05 ± 30.21	3.551 ± 0.8791

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 1,140 investigators of which none were full-time or part-time employees of the sponsor and 24 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1
- Significant payment of other sorts: 20
- Proprietary interest in the product tested held by the investigator: 2
- Significant equity interest held by investigator in sponsor of covered study: 1

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. ABSORB Cohort B

The ABSORB Cohort B trial evaluated the feasibility and performance of the Absorb BVS System (ABSORB Cohort B device) in the treatment of single *de novo* native coronary artery lesions. The ABSORB Cohort B Device is a previous generation of the Absorb GT1 BVS System utilizing a similar Absorb scaffold.

A1. Study Design

ABSORB Cohort B was a prospective, single arm, open-labeled, multi-center, clinical study of 101 subjects enrolled at 12 clinical sites located in Europe, Australia, and New Zealand. The Cohort B was subdivided into two subgroups and different imaging follow-up schedules were applied.

Clinical Inclusion/Exclusion Criteria

Subjects were eligible if they were at least 18 years of age and had evidence of myocardial ischemia (stable or unstable angina, or silent ischemia).

Key angiographic inclusion criteria included: a nominal vessel diameter of 3.0 mm; lesion length ≤ 14 mm; percent diameter stenosis (%DS) of ≥ 50% and < 100%; and TIMI flow of ≥ 1. Key angiographic exclusion criteria included: aorto-ostial location; left main location within 2 mm of the origin of the LAD or LCX; excessive tortuosity; extreme angulation (≥ 90°); heavy calcification; restenosis from previous intervention; target vessel containing thrombus; and other clinically significant lesions in the target vessel or side branch.

Medication and Follow-Up

All subjects were to receive anticoagulation and other therapy during stent implantation according to the standard of care at the clinical site. All subjects were to be maintained on 75 mg clopidogrel daily for a minimum of 6 months and ≥ 75 mg of aspirin daily for the length of the clinical investigation (5 years).

Subjects were evaluated at 30 days, 180 days, 270 days, 12 months, 18 months (subset), 2 years, 3 years, 4 years and 5 years. Subjects in the first group (Group B1) had invasive imaging with qualitative coronary angiography, IVUS, IVUS-VH, and OCT at 6 months, 2 years and 5 years while the second group (Group B2) underwent invasive imaging at 12 months, 3 years and 5 years. Vasomotor function test using nitroglycerin was done at 2, 3, and 5 year follow-up.

Clinical Endpoints

The Absorb Trial Cohort B was an exploratory trial, and there was no primary endpoint for the study. Key endpoints include: Acute success; Major Adverse Cardiac Events (MACE) and Target Vessel Failure (TVF) at each follow-up; in-device and in-segment late loss at 6 months and 2 years; in-device and in-segment Angiographic Binary Restenosis (ABR) rate at 6 months and 2 years by QCA; and in-device mean and minimal lumen area at 6 months and 2 years by IVUS.

A2. Accountability of Subjects

The ABSORB Trial Cohort B registered 101 subjects (Group B1: 45, Group B2: 56) in 12 clinical sites (3 sites in The Netherlands, 2 sites in Australia, 2 sites in New Zealand, 1 site in Belgium, 1 site in Denmark, 1 site in France, 1 site in Poland and 1 site in Switzerland) between March 9, 2009 and November 6, 2009.

A3. Study Population Demographics and Baseline Parameters

A total of 101 subjects are included in the analysis for the full Cohort. The mean age of the full Cohort B subjects (ITT population) was 62.3 ± 8.9 years; 72.3% of subjects were men and 17.0% were current smokers. Diabetic subjects comprised 16.8% of the overall population, 66.0% had hypertension, 25.0% had prior MI, 6.9% had a prior target vessel cardiac intervention, 14.9% presented with unstable angina, and 20.8% had multi-vessel disease.

Based on QCA measurement, the mean lesion length was 9.92 ± 3.65 mm and the mean reference vessel diameter was 2.61 ± 0.37 mm. The pre-procedure MLD was 1.06 ± 0.28 mm and %DS was 59.0 ± 10.0%.

A4. Safety and Effectiveness Results

The clinical results through 5 years are presented in **Table XI-1**. For the ITT population, the MACE rate was 6.9% (7/101) at 1 year (3 NQMIs and 4 ID-TLRs) and 11.0% (11/100) at 5 years (3 NQMIs and 8 ID-TLRs).

Table XI-1 Key Clinical Outcomes of ABSORB Cohort B (ITT Population) through 5 years

	30 days (N=101)	6 month(N=101)	1 year (N=101)	2 year (N=100*)	3 year (N=100*)	4 year (N=100*)	5 year (N=100*)
MACE (COMPOSITE OF SAFETY AND EFFECTIVENESS)	2.0% (2/101)	5.0% (5/101)	6.9% (7/101)	9.0% (9/100)	10.0% (10/100)	10.0 (10/100)	11.0 (11/100)
EFFECTIVENESS							
Ischemia-Driven TLR	0.0% (0/101)	2.0% (2/101)	4.0% (4/101)	6.0% (6/100)	7.0% (7/100)	7.0% (7/100)	8.0% (8/100)
TLR, CABG	0.0% (0/101)	0.0% (0/101)	0.0% (0/101)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)
TLR, PCI	0.0% (0/101)	2.0% (0/101)	4.0% (4/101)	6.0% (6/100)	7.0% (7/100)	7.0% (7/100)	8.0% (8/100)
Ischemia-Driven TVR	0.0% (0/101)	2.0% (2/101)	4.0% (4/101)	8.0% (8/100)	10.0% (10/100)	10.0% (10/100)	11.0% (11/100)
SAFETY							
Cardiac Death	0.0% (0/101)	0.0% (0/101)	0.0% (0/101)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)
All MI	2.0% (2/101)	3.0% (3/101)	3.0% (3/101)	3.0% (3/100)	3.0% (3/100)	3.0% (3/100)	3.0% (3/100)
QMI	0.0% (0/101)	0.0% (0/101)	0.0% (0/101)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)
NQMI	2.0% (2/101)	3.0% (3/101)	3.0% (3/101)	3.0% (3/100)	3.0% (3/100)	3.0% (3/100)	3.0% (3/100)
Scaffold Thrombosis	0.0% (0/101)	0.0% (0/101)	0.0% (0/101)	0.0% (0/95)	0.0% (0/95)	0.0% (0/95)	0.0% (0/95)

* One subject lost to follow-up at 2-year follow-up.

Note: MACE: Cardiac death, MI, ischemia-driven TLR. Note: MI per protocol definition; Q wave MI defined as new pathological Q wave on the ECG; Non-Q wave MI defined as elevation of CK level to ≥ 2 times ULN with elevated CK-MB in the absence of pathological Q-waves.

Follow-up windows in ABSORB Cohort B were: 30 days ± 7 days; 6 months ± 14 days; 1 year ± 28 days; 2 year ± 2 months; 3 year ± 28 days; 4 year ± 28 days; 5 year ± 28 days.

A5. Imaging and Vasomotor Function Results

Intravascular Ultrasound (IVUS) Outcomes

Paired IVUS data at post-procedure, 6-month, 2-year, and 5-year follow-up for 21 lesions from Group 1 subjects are shown in **Table XI-2**, and at post-procedure, 1, 3 and 5 years for 30 lesions from Group 2 subjects are shown in **Table XI-3**. Over the course of 5 years follow-up, there were variable changes in vessel area, scaffold area, lumen area, and plaque area over time between Groups 1 and 2.

Table XI-2 Paired IVUS Results at Post-procedure, 6 Month, 2 Year, and 5 Year (Group 1, ITT Population)

	Post-procedure (L = 21)	6-Month (L = 21)	2-Year (L = 21)	5-Year (L = 21)
Average vessel area (mm^2)	14.56 ± 3.82	14.92 ± 3.78	15.88 ± 4.02	15.28 ± 4.53
Average scaffold area (mm^2)	6.75 ± 1.19	6.63 ± 1.16	7.52 ± 1.79	NA
Average Lumen Area (mm^2)	6.75 ± 1.19	6.59 ± 1.20	7.24 ± 1.91	7.46 ± 2.45
Average Plaque Area (mm^2)	7.81 ± 2.98	8.33 ± 2.88	8.64 ± 2.85	7.75 ± 2.62

Note: Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.

Note: Follow-up windows were: 6 months ± 14 days; 2 year ± 2 months; 5 year ± 28 days

Table XI-3 Paired IVUS Results at Post-procedure, 1, 3, and 5 Year (Group 2, ITT Population)

	Post-procedure (L = 30)	1-Year (L = 30)	3-Year (L = 30)	5-Year (L = 28)
Average Vessel Area (mm^2)	13.61 ± 2.40	14.15 ± 2.61	14.25 ± 2.57	13.23 ± 2.70
Average Scaffold Area (mm^2)	6.31 ± 0.86	6.37 ± 0.97	7.05 ± 1.39	NA
Average Lumen Area (mm^2)	6.31 ± 0.86	6.31 ± 1.01	6.70 ± 1.48	6.48 ± 1.50
Average Plaque Area (mm^2)	7.30 ± 1.85	7.84 ± 1.92	7.55 ± 1.58	6.79 ± 1.90

Note: Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.

Note: Follow-up windows were: 1 year ± 28 days; 3 year ± 28 days; 5 year ± 28 days

In both ABSORB Cohort B1 and B2, Absorb demonstrated good patency out to 5 years.

Optical Coherence Tomography (OCT) Analysis

Serial OCT analysis at baseline, 6 months, 2 and 5 years in 13 lesions from Group 1 are shown in **Table XI-4**, and at baseline, 1, 3 and 5 years for 17 lesions in Group 2 are shown in **Table XI-5**. In both groups, there was an increase in neointimal area

accompanied by an increase in scaffold area, resulting in a stable lumen diameter. Strut coverage by neointima was nearly complete at 6 months and 1 year for Groups 1 and 2.

Table XI-4 Paired OCT Results at Post-procedure, 6 Months, 2 and 5 Years (Group 1, ITT Population)

Group 1 OCT (paired)	Post-procedure (L = 13)	6-month (L = 13)	2-year (L = 13)	5-year (L = 13)
Lumen Area (mm^2)	7.28 ± 1.24	6.04 ± 1.20	6.17 ± 1.44	6.38 ± 1.47
Scaffold Area (mm^2)	7.55 ± 1.17	7.79 ± 1.20	8.54 ± 1.71	N/A
Mean Neointimal Area (mm^2)	NA	1.53 ± 0.36	2.22 ± 0.47	NA
% of Uncovered Struts	96.97 ± 6.83	1.80 ± 1.63	1.40 ± 2.37	NA

Note: Data are presented as Mean ± SD or %. L is the number of lesions with a paired measurement for the specific variable.

Note: Follow-up windows were: 6 months ± 14 days; 2 year ± 2 months; 5 year ± 28 days

Table XI-5 Paired OCT Results at Post-procedure, 1, 3 and 5 Years (Group 2, ITT Population)

Group 2 OCT (paired)	Post-procedure (L = 17)	1-year(L = 17)	3-year (L = 17)	5-year (L = 17)
Lumen Area (mm^2)	7.54 ± 0.88	5.94 ± 1.29	6.01 ± 1.49	5.93 ± 1.53
Scaffold Area (mm^2)	7.61 ± 0.83	7.45 ± 0.84	8.61 ± 1.98	N/A
Mean Neointimal Area (mm^2)	NA	1.42 ± 0.71	2.39 ± 0.68	NA
% of Uncovered Struts	97.65 ± 5.56	3.03 ± 2.81	1.70 ± 1.59	NA

Note: Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.

Note: Follow-up windows were: 1 year ± 28 days; 3 year ± 28 days; 5 year ± 28 days

Although serial IVUS and OCT studies demonstrated late lumen enlargement and an increase in BVS area at 2 years (Group 1) and at 3 years (Group 2), there were some inconsistencies in measurement trends between the imaging modalities (IVUS vs. OCT) and between Groups 1 and 2 at 5 years.

Vasomotor Function Outcomes

At the 3 year follow-up, 27 patients from Group 2 underwent vasomotor function testing with nitrate administration (**Table XI-6**). The in-scaffold mean lumen diameter increased from 2.45 ± 0.37 mm (pre-nitrate) to 2.50 ± 0.39 mm (post-nitrate, p = 0.005). At the 5 year follow-up, 57 patients from the full Cohort B (23 from Group 1 and 34 from Group 2) completed vasomotor function tests with nitrate administration (**Table XI-6**). The in-scaffold mean lumen diameter increased from 2.48 ± 0.38 mm (pre-

nitrate) to 2.56 ± 0.37 mm (post-nitrate administration, $p < 0.0001$). These data indicate that the Absorb-treated segment can vasodilate in response to physiologic stimuli.

Table XI-6 Vasomotor Function by Nitroglycerine Injection at 2, 3 and 5 years (PTE Population)

Mean Luminal Diameter (mm)						
	Group B1 2Y (L=33)		Group B2 3Y (L=47)		Full Cohort 5Y (L=57)	
	Pre-NTG	Post-NTG	Pre-NTG	Post-NTG	Pre-NTG	Post-NTG
Proximal	2.48 ± 0.46	2.65 ± 0.42	2.51 ± 0.39	2.63 ± 0.48	2.53 ± 0.44	2.64 ± 0.43
Distal	2.26 ± 0.41	2.40 ± 0.40	2.28 ± 0.33	2.41 ± 0.35	2.26 ± 0.41	2.39 ± 0.39
Scaffold	2.44 ± 0.37	2.47 ± 0.35	2.45 ± 0.37	2.50 ± 0.39	2.48 ± 0.38	2.56 ± 0.37

Note: Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.

B. ABSORB EXTEND

The ABSORB EXTEND study is a global continued access registry designed to expand treatment with Absorb in a broader patient population including subjects with more complex lesions.

B1. Study Design

ABSORB EXTEND is a prospective, non-randomized, single arm, open-labeled multi-center clinical study that registered 812 subjects at up to 58 global sites. Subjects with a maximum of two *de novo* native coronary artery lesions each located in different epicardial vessels, target lesions between > 22 mm and ≤ 28 mm in length, and reference vessel sizes that were suitable for treatment with Absorb were registered. Treatment by overlapping of two Absorb scaffolds was allowed.

The primary objective of the ABSORB EXTEND trial was to continue the assessment of the safety and performance of Absorb. There was no primary endpoint for the study. The clinical results presented are based on the ITT population

Clinical Inclusion/Exclusion Criteria

Subjects were eligible if they were at least 18 years of age and had evidence of myocardial ischemia (stable or unstable angina, or silent ischemia). Subjects with target vessel diameter of ≥ 2.0 mm and ≤ 3.3 mm by on-line quantitative coronary angiography (QCA) or IVUS, lesion length ≤ 28 mm, %DS of ≥ 50% and < 100%, and TIMI flow of

≥ 1 could be registered. Key angiographic exclusion criteria included: aorto-ostial location; left main location; lesions within 2 mm of the origin of the LAD or LCX; excessive tortuosity; extreme angulation (≥ 90°); heavy calcification; evidence of myocardial bridging; restenosis from previous intervention; target vessel containing thrombus; and other clinically significant lesions in the target vessel or side branch.

PCI for other lesions in a non-target vessel could be done ≥ 30 days prior to or if planned to be done 6 months after the index procedure. PCI for other lesions in the target vessel could be done > 6 months prior to or if planned to be done 6 months after the index procedure.

Medication and Follow-Up

Subjects who were not on chronic antiplatelet or aspirin therapy were required to receive a loading dose of a P_2Y_{12} platelet inhibitor (≥ 300 mg of clopidogrel, ≥ 60 mg of prasugrel, or 180 mg of ticagrelor) and aspirin ≥ 300 mg 6 to 72 hours prior to the index procedure, but no later than 1 hour after the procedure. All patients were to be maintained on 75 mg clopidogrel daily or 10 mg of prasugrel daily, or 90 mg twice daily of ticagrelor for a minimum of 6 months and ≥ 75 mg of aspirin daily for the length of the clinical investigation.

Subjects are evaluated at 30 days, 180 days, 12 months, 18 months (subset), 2 years and 3 years.

Clinical Endpoints

Key clinical endpoints include: Acute success, Major Adverse Cardiac Event (MACE), Target Lesion Failure and Target Vessel Failure (TVF) and the components of the composites at each follow-up assessment time point.

B2. Accountability of Subjects

ABSORB EXTEND registered 812 subjects between January 11, 2010 and October 2, 2013. A total of 874 lesions were treated, with 7.6% (62/812) of the subjects with two target lesions treated and 10.5% (85/812) with long lesions treated with planned overlapping Absorb scaffolds. One-year data are available for all 812 subjects.

B3. Study Population Demographics and Baseline Parameters

The mean age was 61.1 ± 10.8 years, 74.3% (603/812) were male, 23.2% (188/812) were tobacco users, 69.3% (563/812) had hypertension requiring medication, 67.7% (550/812) had dyslipidemia requiring medication, 28.5% (230/807) had prior MI, and 26.5% (215/812) were diabetic.

B4. Safety and Effectiveness Results

The clinical results for the ITT population through 3 years are presented in **Table XI-7**. The composite endpoint of TLF used the protocol World Health Organization (WHO) definition for MI and is based on hierarchical counts. The TLF composite rate for ABSORB EXTEND was 5.1% (41/811) at 1 year, 6.9% (56/807) at 2 years and 9.0% (55/613) at 3 years. Note that not all subjects have reached 3-year follow-up.

Table XI-7 ABSORB EXTEND Clinical Results through 3 years (ITT population

	ABSORB EXTEND (N=812)		
	1-Year	**2-Year**	**3-Year**
TLF	5.1% (41/811)	6.9% (56/807)	9.0% (55/613)
Cardiac Death	0.7% (6/811)	1.1% (9/807)	1.5% (9/613)
TV-MI	3.3% (27/811)	4.2% (34/807)	5.2% (32/613)
ID-TLR	2.3% (19/811)	4.1% (33/807)	4.9% (30/613)
Definite/Probable Stent/Scaffold Thrombosis	1.0% (8/808)	1.5% (12/799)	2.0% (12/603)

Note: 1-year timeframe includes a window of ± 28 days

Note: N is the total number of subjects

Note: MI per protocol definition per WHO; WHO definition of MI: Q wave MI defined as new pathological Q wave on the ECG; Non-Q wave MI defined as elevation of CK level to ≥ 2 times ULN with elevated CK-MB in the absence of new pathological Q-waves.

C. ABSORB II Randomized Controlled Trial

The ABSORB II Randomized Controlled Trial (ABSORB II) is the CE mark post-approval randomized clinical, and the first trial comparing Absorb to XIENCE. ABSORB II was designed to compare the safety, effectiveness and performance of Absorb compared to XIENCE in the treatment of *de novo* native coronary artery lesions.

C1. Study Design

The ABSORB II is a prospective, randomized (2:1 Absorb to XIENCE), active-controlled, single-blinded, multicenter clinical trial (Europe and New Zealand) that registered 501 subjects at 46 sites. Target lesions were up to 2 *de novo* native coronary artery lesions, each located in different major epicardial vessels, all with an angiographic maximal luminal diameter between 2.25 mm and 3.8 mm measured by on-line quantitative coronary angiography (QCA), and a lesion length of ≤ 48 mm. Planned overlapping of study devices was allowed for treatment of long lesions.

The co-primary endpoints are vasomotor function assessed by the change in mean lumen diameter between pre- and post-nitrate infusion at 3 years (superiority) and minimum lumen diameter changes from post-procedure to 3 years (non-inferiority, reflex to superiority), both measured by angiography.

Clinical Inclusion and Exclusion Criteria

Patients were eligible if they were at least 18 years of age and less than 85 years of age and had evidence of myocardial ischemia. Key angiographic inclusion criteria included: vessel D_{max} by on-line QCA of ≥ 2.25 mm and ≤ 3.8 mm and lesion length ≤ 48 mm; %DS of $\geq 50\%$ and $< 100\%$; and TIMI flow of ≥ 1. Key angiographic exclusion criteria included: aorto-ostial location; left main location; location within 2 mm of the origin of the LAD or LCX; excessive tortuosity ($\geq$ two 45° angles); extreme angulation ($\geq 90°$); heavy calcification proximal to or within the target lesion; myocardial bridge; restenosis lesion; target vessel containing thrombus; bifurcation lesions with side branch ≥ 2 mm in diameter or with a side branch < 2 mm in diameter requiring guide wire protection or dilatation.

Medication and Follow-Up

Subjects were required to receive a loading dose of aspirin (250-500 mg) and an ADP antagonist (300-600 mg of clopidogrel or 60 mg of prasugrel) 0 to 72 hours prior to the index procedure or 1 hour after the end of the procedure. The loading dose could be omitted for those subjects on chronic therapy for ≥ 7 days prior to the index procedure. All subjects were to be maintained on an ADP antagonist (≥ 75 mg of clopidogrel, or ≥ 10 mg of prasugrel, or ≥ 90 mg ticagrelor twice daily) for a minimum of 180 days, and aspirin (≥ 75 mg) for 5 years following the index procedure.

Clinical follow-up is planned at 30 days, 180 days and at 1, 2, 3, 4 and 5 years. All subjects undergo coronary angiography, IVUS (gray-scale and IVUS-VH) at pre- and post-device implantation and at 3-year follow-up. A Multi Slice Computed Tomography (MSCT) scan will be performed in all Absorb subjects at 3 years follow-up.

Endpoint Assessments

The co-primary endpoints are vasomotor function assessed by the change in mean lumen diameter between pre- and post-nitrate administration at 3 years (superiority) and minimum lumen diameter changes from post-procedure to 3 years (non-inferiority, reflex to superiority), both assessed by angiography. The major secondary endpoint is in-scaffold/in-stent mean lumen area change, from post-procedure to 3 years by IVUS. Other traditional clinical endpoints of coronary stent trials are also evaluated at each clinical follow-up time point and customary angiographic and IVUS endpoints are evaluated at post-procedure and at 3 years. Quality of life will be assessed pre-procedure, and post-procedure at 180 days, and annually through 5 years, using the SF-

12 Health Survey, the EuroQoL 5D (EQ-5D), and the Seattle Angina Questionnaire (SAQ).

Clinical outcomes in the ITT population through 2 years are available and presented.

C2. Accountability of Subjects

Between Nov 28th, 2011, and June 4th, 2013, 501 subjects were registered in the ABSORB II trial and randomly assigned to the Absorb arm (335 subjects) or the XIENCE arm (166 subjects). A total of 364 lesions were treated in the Absorb arm, and 182 lesions in the XIENCE arm. Early termination at 1 year, due to consent withdrawal or death, affected 1.8% (6/335) of the subjects in the Absorb arm and 1.2% (2/166) in the XIENCE arm, and 2 years follow-up includes 96.7% of the Absorb group and 98.2% for the XIENCE group. All subjects have completed 2-year follow-up, and clinical follow-up through 5 years is ongoing.

C3. Study Population Demographics and Baseline Parameters

The mean age was 61.5 ± 10.0 and 60.9 ± 10.0 years in the Absorb arm and XIENCE arms, respectively. The patient population consisted of predominately males, 75.5% in the Absorb arm and 79.5% in the XIENCE arm. There was high prevalence of hypertension (69.0% vs. 71.7% for the Absorb and XIENCE arms, respectively) and dyslipidemia (75.2% vs. 80.1% for the Absorb and XIENCE arms, respectively). Over 20% of the population were diabetic (23.9% vs. 24.1% for the Absorb and XIENCE arms, respectively).

C4. Safety and Effectiveness Results

No patients have yet reached the primary imaging endpoint at 3-years follow-up. Safety and effectiveness results in the ITT population through 2 years are presented in **Table XI-8**. At 1-year, the TLF rate was 4.8% (16/331) in the Absorb arm and 3.0% (5/165) in the XIENCE arm, and the definite/probable stent/scaffold thrombosis rate was 0.9% (3/329) in the Absorb arm and 0.0% (0/164) in the XIENCE arm. At 2 years, the TLF rate was 7.0% (23/328) in the Absorb arm and 3.0% (5/164) in the XIENCE arm, and the definite/probable stent/scaffold thrombosis rate was 1.5% (3/325) in the Absorb arm and 0.0% (0/163) in the XIENCE arm.

Table XI-8 ABSORB II Clinical Results (ITT Population) through 2 Years

	ABSORB II (N=501)			
	1-Year		**2-Year**	
	Absorb N=335	**XIENCE N=166**	**Absorb N=335**	**XIENCE N=166**
TLF	4.8% (16/331)	3.0% (5/165)	7.0% (23/328)	3.0% (5/164)
Cardiac Death	0.0% (0/331)	0.0% (0/165)	0.6% (2/328)	0.0% (0/164)

	ABSORB II (N=501)			
	1-Year		2-Year	
	Absorb N=335	XIENCE N=166	Absorb N=335	XIENCE N=166
TV-MI	4.2% (14/331)	1.2% (2/165)	5.2% (17/328)	1.2% (2/164)
ID-TLR	1.2% (4/331)	1.8% (3/165)	2.7% (9/328)	1.8% (3/164)
Definite/Probable Stent/Scaffold Thrombosis	0.9% (3/329)	0.0% (0/164)	1.5% (5/325)	0.0% (0/163)

Note: 1-year timeframe includes a window of ± 28 days

Note: N is the total number of subjects

Note: MI is per protocol definition: Q wave MI defined as new pathological Q wave on the ECG; Non-Q wave MI defined as elevation of CK level to ≥ 2 times ULN with elevated CK-MB in the absence of new pathological Q-waves.

D. ABSORB Japan Randomized Controlled Trial

The ABSORB Japan Randomized Controlled Trial (ABSORB Japan) is the randomized pivotal trial to support the approval of Absorb in Japan. The objective of ABSORB Japan is to compare the safety and effectiveness of Absorb in Japanese subjects with ischemic heart disease caused by *de novo* native coronary artery lesions to the approved XIENCE stent.

D1. Study Design

ABSORB Japan is a prospective, randomized (2:1 Absorb to XIENCE), active-controlled, single-blinded, multicenter clinical trial that registered 400 subjects. Treatment of up to 2 *de novo* native coronary artery lesions was permissible, with each lesion located in different major epicardial vessels, with a D_{max} of ≥ 2.5 mm and ≤ 3.75 mm and a lesion length of ≤ 24 mm (by visual estimation). Planned overlapping treatment of the target lesion was not allowed. If a subject had only one target lesion eligible to be treated with the study device, the additional non-target lesion could be treated with XIENCE. Subjects were assigned to one of three intravascular imaging subgroups, IVUS (150 subjects), OCT 1 (125 subjects), or OCT 2 (125 subjects) based on the imaging modality and schedule of follow-up intravascular imaging.

Absorb was available in diameters of 2.5, 3.0, and 3.5 mm and lengths of 8, 12, 18 and 28 mm (the 8 mm length was not available for 3.5 mm diameter). All commercial sizes and diameters of XIENCE were available except for the 2.25 mm diameter and the 33 and 38 mm lengths. Overlap with same device as assigned was allowed in the case of bailout.

The primary endpoint of the study is TLF (composite of cardiac death, myocardial infarction attributable to target vessel, or ischemia-driven target lesion revascularization)

at 1 year. The hypothesis test was designed to show non-inferiority of Absorb to XIENCE with a pre-specified non-inferiority margin of 8.6% using the likelihood score method by Farrington and Manning at a one-sided alpha of 0.05.

Clinical Inclusion/Exclusion Criteria

Subjects were eligible if they were at least 20 years of age and had evidence of myocardial ischemia Prior PCI to the target vessel ≤ 12 months or to the non-target vessel ≤ 24 hours (if successful and uncomplicated) or ≤ 30 days, or planned PCI either in target or non-target vessels after the index procedure were not allowed.

Key angiographic inclusion criteria included: D_{max} of ≥ 2.5 mm and ≤ 3.75 mm and lesion length ≤ 24 mm; % diameter stenosis (%DS) of ≥ 50% and < 100%; TIMI flow of ≥ 1 by visual estimation. Key angiographic exclusion criteria included: aorto-ostial location; left main location; location within 2 mm of the origin of the LAD or LCX; excessive tortuosity (≥ two 45° angles); extreme angulation (≥ 90°); heavy calcification proximal to or within the target lesion; myocardial bridge; restenosis lesion; target vessel containing thrombus; bifurcation lesion with side branch ≥ 2 mm in diameter requiring protection guide wire or requiring dilatation. Successful pre-dilatation with < 40% residual %DS and TIMI-3 flow (without angiographic complications, dissections, or chest pain or ST changes > 5 minutes in duration) were required.

Medication and Follow-Up

Subjects received a loading dose of aspirin and an ADP antagonist (clopidogrel or ticlopidine) per site standard dose and schedule. A loading dose could be omitted for those subjects on chronic therapy for ≥ 4 days. All subjects were to be maintained on an IFU-specified dose of ADP antagonist for a minimum of 12 months, and aspirin (80 mg) for an indefinite period after index procedure.

Clinical follow-up is planned at 30 days, 180 days, and at 1, 2, 3, 4 and 5 years. All subjects are to undergo follow-up coronary angiography at 13 months and at 3 years. The IVUS subgroup will undergo IVUS follow-up at post-procedure and 3 years. The OCT 1 subgroup will undergo OCT follow-up at post-procedure, 2 and 3 years. The OCT 2 subgroup will undergo OCT follow-up only at 3 years (no post-procedure OCT). Additional evaluations in selected sites include a MSCT scan at 13 months and 3 years (150 subjects) and an ACh-induced vasoreactivity test at 4 years (120 subjects).

Clinical Endpoints

The primary endpoint is TLF (composite of cardiac death, myocardial infarction attributable to target vessel, or ischemia-driven target lesion revascularization) at 1 year. Powered secondary endpoints include in-segment late loss (LL) at 13 months by angiography, in-device mean lumen area change from post-procedure to 3 years by IVUS, and in-device mean lumen diameter change between pre- and post-nitrate infusion at 3 years by angiography. The powered secondary endpoint of in-segment LL

will be tested for non-inferiority (Absorb vs. XIENCE, non-inferiority margin of 0.195 mm) using an asymptotic test at one-sided alpha of 0.05. For the powered imaging secondary endpoints of vasomotor function and change of mean lumen area (superiority, Absorb vs. XIENCE), the pooled subjects from the Imaging Cohort of ABSORB III and ABSORB Japan are to be used, and superiority tests will be performed using a t-test at a two-sided alpha of 0.025.

Traditional clinical endpoints in coronary stent trials will also be evaluated at each clinical follow-up time point.

D2. Accountability of Subjects

Between April 27th, 2013 and December 27th, 2013, 400 subjects from 38 investigational sites in Japan were registered in the ABSORB Japan, and randomly assigned to the Absorb arm (266 subjects) or the XIENCE arm (134 subjects). A total of 275 lesions were treated in the Absorb arm, and 137 lesions in the XIENCE arm. Early termination at 1 year, due to consent withdrawal or death, affected 4 subjects in the Absorb arm and 1 subject in the XIENCE arm. Two subjects (1 in the Absorb arm and 1 in the XIENCE arm) who withdrew consent but had no known DMR (Death, MI, Revascularization) event were excluded from the analysis. All subjects have completed their 1-year follow-up and clinical follow-up through 5 years is ongoing.

D3. Study Population Demographics and Baseline Parameters

The mean age was 67.1 ± 9.4 years in the Absorb arm and 67.3 ± 9.6 years in the XIENCE arm. The population of the ABSORB Japan was predominantly male (78.9% in the Absorb arm, 73.9% in the XIENCE arm). In the study population, there was a high prevalence of comorbidities of hypertension (78.2% vs 79.9% for the Absorb and XIENCE arms, respectively) and dyslipidemia (82.0% vs 82.1% for the Absorb and XIENCE arms, respectively). Over 30% of the population was diabetic (36.1% vs 35.8% for the Absorb and XIENCE arms, respectively). The proportion of patients with two (or more) lesions treated were 10.9% (29/266) in the Absorb arm and 9.7% (13/134) in the XIENCE arm.

D4. Safety and Effectiveness Results

The safety and efficacy results for the ABSORB Japan are presented in **Table XI-9**. The observed TLF rate at one year was 3.8% (5/133) in the XIENCE arm and 4.2% (11/265) in the Absorb arm (difference 0.39%, 05% CI -4.68% to 4.18%), which met statistical non-inferiority ($p < 0.0001$). The observed definite/probable stent/scaffold thrombosis rate at 1-year was 1.5% for both Absorb and XIENCE arms.

Table XI-9 ABSORB Japan Clinical Results (ITT Population) – 1-Year Results

	Absorb (N=266)	**XIENCE (N=134)**
TLF (COMPOSITE OF SAFETY AND EFFECTIVENESS)	4.2% (11/265)	3.8% (5/133)
EFFECTIVENESS		
Ischemia-Driven TLR	2.6% (7/265)	2.3% (3/133)
TLR, CABG	0.0% (0/265)	0.0% (0/133)
TLR, PCI	2.6% (7/265)	2.3% (3/133)
Ischemia-Driven TVR	4.9% (13/265)	3.8% (5/133)
SAFETY		
All Death	0.8% (2/265)	0.0% (0/133)
Cardiac Death	0.0% (0/265)	0.0% (0/133)
Vascular Death	0.4% (1/265)	0.0% (0/133)
Non-cardiovascular Death	0.4% (1/265)	0.0% (0/133)
TV-MI	3.4% (9/265)	2.3% (3/133)
QMI	1.1% (3/265)	0.0% (0/133)
NQMI	2.3% (6/265)	2.3% (3/133)
All MI	3.4% (9/265)	2.3% (3/133)
QMI	1.1% (3/265)	0.0% (0/133)
NQMI	2.3% (6/265)	2.3% (3/133)
Cardiac Death or MI	3.4% (9/265)	2.3% (3/133)
Cumulative ARC-defined Definite + Probable Stent/Scaffold Thrombosis (0-365 days)	1.5% (4/262)	1.5% (2/133)
Acute (≤ 1 day)	0.0% (0/266)	0.0% (0/133)
Sub-Acute (> 1-30 days)	1.1% (3/265)	0.8% (1/133)
Late (31-365 days)	0.4% (1/262)	0.8% (1/133)

Note: 1-year timeframe includes a window of ± 28 days

Note: N is the total number of subjects

Note: MI is per protocol definition; Q-wave MI is defined as development of new, pathological Q wave on the ECG in ≥ 2 contiguous leads. Non Q-wave MI is defined as CK-MB > 5X ULN for peri-procedural MI (≤ 48 hrs post-PCI); CK-MB or Troponin > ULN plus evidence of ischemia for spontaneous MI.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on March 15, 2016, the Circulatory Systems Device voted 9-1 that there is reasonable assurance the device is safe, 10-0 that there is reasonable assurance that the device is effective, and 9-0 (with one abstention) that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication.
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm485091.htm

B. FDA's Post-Panel Action

Following review of data from the ABSORB III pivotal trial, and taking into account the recommendations of the Advisory Panel, FDA has determined that in patients with a visually estimated target vessel RVD < 2.5 mm the probable benefits of deploying an Absorb GT1 BVS do not exceed the probable risks. While such usage would not be in compliance with the proposed indications, FDA believes that for patient safety, it will be important to alert interventionists to the increased risk for MI and scaffold thrombosis resulting from the off-label usage of Absorb BVS in undersized vessels. The proposed IFU should contain appropriate precaution and warnings in this regard, and to further mitigate this risk, FDA supports the sponsor's proposal to strongly advise the use of adjunctive quantitative imaging modalities (IVUS, OCT or online QCA) for all vessels with visually estimated RVD < 2.75 mm. FDA supports the sponsor's plan to provide a mandatory training program in conjunction with the commercial roll-out of the Absorb GT1 BVS, with a focus on appropriate target vessel size selection and optimal procedural techniques. In addition to the ongoing ABSORB IV RCT, a newly enrolled 3,000 patient post-approval study will gather important post-market clinical follow-up information (to include rates of cardiac death, MI, and scaffold thrombosis). An imaging core lab will review the angiograms from 500 patients enrolled in the post-approval study in order to ensure that the training regimen effectively guides operators to identify a target vessel RVD appropriate for Absorb deployment (QCA assessed RVD ≥ 2.25 mm).

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The principal safety and effectiveness information for the Absorb GT1 BVS System is derived from preclinical studies and from ABSORB III and is supported by data from ABSORB Cohort B, ABSORB EXTEND, ABSORB II, and ABSORB Japan. In addition, the safety of everolimus, the drug eluted from the Absorb scaffold, was evaluated in the ABSORB III PK sub-study.

The preclinical assessment is based on results obtained from the following testing: biocompatibility; *in vivo* pharmacokinetics; *in vitro* engineering testing; coating

characterization; chemistry, manufacturing and controls information; *in vivo* animal testing; sterilization; and stability testing. These tests revealed the following information:

Biocompatibility testing, *in vivo* pharmacokinetics, and *in vivo* animal testing demonstrate that the acute and chronic *in vivo* performance characteristics of the product provide a reasonable assurance of safety and acceptability for clinical use.

The *in vivo* engineering testing conducted on Absorb and its delivery system(s) demonstrated that the performance characteristics met the product specifications and the coating characterization testing adequately described the important attributes of the everolimus/polymer coating. The chemistry, manufacturing, and controls information ensures that product meeting specifications will be released.

The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The stability testing demonstrated that the product can be labeled with a shelf life of 12 months.

A. Effectiveness Conclusions

In the pivotal ABSORB III trial, Absorb met the primary target lesion failure (TLF, a composite of safety and effectiveness) endpoint of non-inferiority compared to XIENCE at 1 year, with rates of 7.8% in the Absorb arm and 6.1% in the XIENCE arm (non-inferiority p-value = 0.007). This satisfies the regulatory standard for DES approval by demonstrating a reasonable assurance of safety and effectiveness. Absorb was effective with ID-TLR rates comparable to XIENCE (Absorb: 3.0% vs. XIENCE: 2.5%). Absorb did not meet the superiority endpoint vs. XIENCE for recurrent angina at 1 year. However, the rates of for recurrent angina and the other 1-year revascularization endpoints (ID-TVR and all revascularization) were comparable between the Absorb and XIENCE groups.

B. Safety Conclusions

As noted above, in the pivotal ABSORB III trial, Absorb met the primary TLF endpoint, a composite of safety and efficacy elements, compared to XIENCE (non-inferiority at 1-year). The safety endpoints included all-cause death, cardiac death, all MI, MI attributable to the target vessel (TV-MI) and stent/scaffold thrombosis (**Section X-D**). For all safety endpoints evaluated at 30 days or at 1 year, outcomes were comparable in both treatment groups although the observed numerical event rates were slightly higher in the Absorb group. An ABSORB III post-hoc analysis (**Section X-D3**) identified a safety signal when Absorb was implanted in QCA-assessed vessels < 2.25 mm in diameter; there was a greater difference in the observed numerical rates for TV-MI and device thrombosis in favor of XIENCE vs. Absorb than what was seen in the overall ITT population. In QCA-assessed vessels ≥ 2.25 mm in diameter, the rates of TV-MI and device thrombosis for Absorb and XIENCE were comparable.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The totality of the data from the Absorb clinical studies satisfy FDA's regulatory approach for approval for new coronary stents or scaffolds. In particular, in the ABSORB III randomized trial, Absorb was shown to be non-inferior to a high quality standard of care (XIENCE) for the combined safety and effectiveness composite endpoint of TLF at 1 year. The outcomes of the ABSORB III trial demonstrate that Absorb preserves the effectiveness of DES over bare metal stents, provides a reasonable assurance of safety and effectiveness as compared to current generation DES, and offers an absorbable coronary revascularization treatment option for patients.

The ABSORB III trial results provide evidence that Absorb improves coronary luminal diameter in patients with ischemic heart disease due to *de novo* native coronary artery lesions. A metric used to measure the benefit is the percentage of patients who were event-free at 1 year post-procedure. For the primary endpoint of TLF, 92.2% of Absorb patients were free of a TLF event at 1 year. For the secondary endpoints at 1 year, 82% of patients were free of angina, 91% of patients were free of all revascularization and 95% of patients were free of ischemia-driven target vessel revascularization. Based on the percentage of patients who were event free at 1 year, there is a high probability that patients intended to be treated with Absorb will experience a benefit.

The ABSORB III trial was designed to evaluate the safety and effectiveness of Absorb compared to XIENCE in the treatment of subjects with ischemic heart disease caused by up to two *de novo* native coronary artery lesions in separate epicardial vessels. The data from ABSORB III are considered robust, as it was a large prospective, randomized (2:1 Absorb BVS vs XIENCE), single-blind, multi-center trial of 2,008 randomized patients. There was a high level of oversight in the ABSORB III trial which included trial monitoring and an independent angiographic core laboratory, clinical events committee, and data safety monitoring board. The follow-up rate of subjects at 1 year in ABSORB III was 99%. The ABSORB III trial showed that Absorb was non-inferior to XIENCE for the primary endpoint of TLF at 1-year. Absorb clinical outcomes observed in supplementary studies (ABSORB Japan, ABSORB II, Cohort B and ABSORB EXTEND) were generally similar to ABSORB III.

Additional factors to be considered in determining probable risks and benefits for the Absorb GT1 BVS System device include: characterization of the disease, availability of alternative treatments, quality of the study design and conduct, robustness of analysis of study results, and risk mitigation. Coronary artery disease (CAD) can be accompanied by symptomatic chest pain or silent ischemia which affects patient's quality of life. CAD is treatable, but if left untreated, the condition can progress to further stenosis within the arteries, increased symptoms, and the need for revascularization. Available treatments for CAD include medical therapy, percutaneous coronary angiography (PCI) and coronary artery bypass graft (CABG) surgery. In comparison to medical therapy, PCI has been shown to reduce the incidence of angina. The patients treated in ABSORB

III represent a standard PCI population. Based on the ABSORB III trial results, Absorb provides an appropriate treatment option.

In summary, the data in ABSORB III support safety and effectiveness of Absorb through 1 year. In addition, clinical results at 1 year and limited data beyond 1 year from non-US ABSORB clinical studies support Absorb safety and effectiveness. Patients in ABSORB III will be followed through 5 years, and the ABSORB IV trial will provide data on an additional 1,500 Absorb patients through 5 years. Finally, the ABSORB USA post-approval study will provide clinical data on approximately newly enrolled 3,000 patients.

The risks associated with Absorb are similar to those associated with standard PCI and current generation approved DES. In the post-hoc RVD analysis, numerically higher event rates were observed in both treatment arms when used in small vessels (QCA-assessed RVD < 2.25 mm) but with relatively higher event rates for Absorb compared to XIENCE. To address the observed safety concern in subjects with QCA-assessed vessels < 2.25 mm (including diabetics) and to mitigate risk, the Absorb instructions for use will include specific warnings, precautions, and recommendations regarding the importance of vessel sizing to identify arteries that are appropriate for Absorb implantation.

In conclusion, given the available information, the data support that for improving coronary luminal diameter in patients with ischemic heart disease due to *de novo* native coronary artery lesions (length ≤ 24 mm) with a reference vessel diameter of ≥ 2.5 mm and ≤ 3.75 mm, the probable benefits of Absorb outweigh the probable risks.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use (i.e., those with ischemic heart disease due to *de novo* native coronary artery lesions (length ≤ 24 mm) with a reference vessel diameter of ≥ 2.5 mm and ≤ 3.75 mm). This conclusion is based on the 1 year clinical endpoint results of the US pivotal ABSORB III trial, supported by additional data from ABSORB Cohort B, ABSORB EXTEND, ABSORB II, and ABSORB Japan.

XIV. CDRH DECISION

CDRH issued an approval order on July 5, 2016. The final conditions of approval cited in the approval order are described below.

1. ODE Lead PMA Post-Approval Study – ABSORB IV Randomized Controlled Trial: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The ABSORB IV Randomized Controlled Trial is a prospective randomized controlled trial that will enroll 3,000 subjects, randomized 1:1 to the BVS or the XIENCE stent. The primary endpoints of the ABSORB IV RCT are: (1) the percentage of patients who experienced angina within 1 year; and (2) the target lesion failure (TLF) rate between 1 and 5 years (landmark analysis).

   You must collect and report to the Agency clinical outcomes through 5 years post-procedure on subjects enrolled in the ABSORB III and ABSORB IV trials. When appropriate or as requested by FDA, you should submit PMA supplements requesting approval to update your Instructions for Use (IFU) to include follow-up data from these trials.

2. OSB Lead PMA Post-Approval Study – ABSORB USA Post-Approval Clinical Study: The Office of Surveillance and Biometrics (OSB) will have the lead for studies initiated after device approval. The ABSORB USA Post-Approval Clinical Study is a prospective, open-label, multi-center evaluation of the PMA-approved, commercially-distributed Absorb GT1 BVS.

   You must conduct a prospective, open-label, multi-center evaluation of the PMA-approved, commercially-distributed Absorb GT1 BVS consisting of at least 3,000 US patients that receive the device post-approval. The effort should assess the rate of GT1 BVS thrombosis and the rate of cardiac death plus myocardial infarction (MI) through one year, according to the clinical follow-up schedule in patients treated with the Absorb GT1 BVS according to its labeled indications for use. The rates of GT1 BVS thrombosis and cardiac death/MI should also be evaluated in patients treated with the Absorb GT1 BVS through 3-years post-procedure, according to the clinical follow-up schedule.

   You must provide an operator training program that includes an assessment plan to evaluate the effectiveness of training on the recommended procedure for Absorb GT1 BVS implantation. Within the post-approval effort as part of this training program, you must conduct an angiographic sub-analysis of at least 500 patients consecutively implanted by inexperienced Absorb GT1 BVS operators to assess the selection of appropriately sized coronary arteries for GT1 BVS implantation. For this angiographic sub-analysis, you should provide quarterly interim progress reports to FDA.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1. Kovarik, J.M., et al., Everolimus in *de novo* cardiac transplantation: pharmacokinetics, therapeutic range, and influence on cyclosporine exposure. J Heart Lung Transplant, 2003. 22(10): p. 1117-25.

2. Starling, R.C., et al., Therapeutic drug monitoring for everolimus in heart transplant recipients based on exposure-effect modeling. Am J Transplant, 2004. 4(12): p. 2126-31